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SATURDAY NOVEMBER 18 1944

TABLE OF CONTENTS

Prevention of Post-Arsphenamine Jaundice J. BEATTIE, M.D., and J. MARSHALL, M.B. 651

Acute Perforated Peptic Ulcer in the West of Scotland—II
C. F. W. ILLINGWORTH, F.R.C.S., L. D. W. SCOTT, M.R.C.P., and R. A. JAMIESON, F.R.C.S. 655

The Giant Magnet in Ophthalmic Battle Casualties
R. E. WRIGHT, M.Ch., and H. A. G. DUNCAN, M.D. 658

Latent Mastoiditis in Infancy W. H. PATTERSON, M.D., and G. STEWART SMITH, M.D.....659

Secondary Abdominal Pregnancy FRANCIS E. STOCK, F.R.C.S. 661

MEDICAL MEMORANDA

Gas Gangrene after Amputation under Refrigeration Anaesthesia: A Warning. E. KIRZ. M.D. 662

GENERAL ARTICLES AND NEWS

The Portraits of William Harvey. GEOFFREY KEYNES, F.R.C.S. 669

Mepacrine for Malaria: Statement by M.R.C. Committee 664

Retractor for Prostatic Pouch. C. E. KINDERSLEY, F.R.C.S. 663

MEDICAL RESEARCH IN S. AFRICA 664

INDUSTRIAL MEDICINE AND HEALTH ...670

EMPIRE CANCER CAMPAIGN 670

THE SERVICES 676

UNIVERSITIES AND COLLEGES 677

MEDICAL NOTES IN PARLIAMENT 677

MEDICAL NEWS 678

REVIEWS

Survey of Biochemistry 662

An Adventurous Life 663

Endometriosis 663

Notes on Books 663

OBITUARY

Raymond Johnson, F.R.C.S. 676

Greville MacDonald, M.D. 676

Frederick Walker, M.R.C.S. 677

J. A. Davidson, M.D. 677

LEADING ARTICLES

The Rise in Peptic Ulcer.....665

Mepacrine and Malaria.....666

ANNOTATIONS

Sulphonamides and Agranulocytosis...667

Health Services in N. Ireland 668

Food Yeast 668

The Health of Manchester 668

LETTERS AND ANSWERS

Water Testing—Insulin to Increase Weight—Liver Function Tests—Bacterial Enteritis—Intravenous Anaesthetics—Local Authorities and Dance Halls—Rheumatoid Arthritis and B.S.R.—Pre-menstrual Psychology—Treatment of an Epileptic—Combining Vitamins—Sodium Morrhuate for Ganglion—Penicillin and Poliomyelitis—Pethidine—Effects of Stilboestrol—Iron and Constipation—Xerodermia—Demobilization of Medical Students—Diagnosis of Minimal Hyperthyroidism—Smoking and Nicotine Dosage 680-2

SUPPLEMENT

Proceedings of Council.....113

General Practice in New Zealand.....115

Panel Conference Resolutions.....117

CORRESPONDENCE 119

RETURN TO CIVILIAN PRACTICE 122

ANTIFREEZE MIXTURES 122

BRANCH AND DIVISION MEETINGS 122

CORRESPONDENCE

Arsenic in Malaria. D. B. BLACKLOCK, M.D. 671

Time of Ovulation. F. DAVIES, M.D. 671

Industrial Dermatitis. A. C. ROXBURGH, M.D. 672

Artificial Insemination. ROBERT FORBES, M.B. 672

The Hazard of Anaesthesia. J. H. HANNAN, M.D. 672

Drugs and the Doctor. H. N. LINSTEAD, M.P. 672

Rate of Artificial Respiration in Cyanosis. P. R TINGLEY, M.B. 673

Atmospheric Conditions and Group Recurrences. J. H. D. WEBSTER, M.D. 674

Mistaken Diagnoses in Infectious Fevers. A. G. BADENOCH, M.D. ...674

Débridement. C. MAX PAGE, F.R.C.S. 674

"Skiagram." H. B. PADWICK, M.B. 674

Mr. Shaw on Doctors. H. J. STARLING, M.D.; G. L. DAVIES, M.R.C.S. 675

Psychology of the "Presser." W. BARLOW, B.M. 675

Association of Municipal Specialists. G. F. STEBBING, F.R.C.S. 675

Registration of Specialists. GEORGE MACDONALD, M.D. 675

Mental Health Service. W. G. MASEFIELD, M.R.C.S. 676

Epidemiology Section.....679

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 18 1944

STUDIES ON HEPATIC DYSFUNCTION

II. THE VALUE OF SULPHUR-CONTAINING AMINO-ACIDS AND CASEIN DIGEST IN THE PREVENTION OF POST-ARSPHENAMINE JAUNDICE

BY

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Miller and Whipple (1942) observed that in protein-depleted dogs chloroform anaesthesia was followed by fatal liver damage. This damage could be averted completely by the administration of methionine before anaesthesia. These observations suggested to us that the liver damage which occurs during an attack of post-arsphenamine jaundice might be averted by some similar treatment.

We have pointed out before (Beattie and Marshall, 1944) that in a clinic under the supervision of one of us the incidence of post-arsphenamine jaundice during the years 1942 and 1943 was over 50% of all cases treated entirely at the clinic. The incidence did not vary from month to month. Moreover, the time of greatest incidence of the disease lay between the 13th and 19th weeks after starting arsenical therapy. In view of these observations it seemed worth while to attempt a series of experiments to determine if methionine, or any of the other sulphur-containing amino-acids, or casein digests rich in methionine, would exert some demonstrable protective effect against post-arsphenamine jaundice during the time when the disease was most frequently developed. Apart from the scientific interest of such a study, a positive result would have some immediate practical value. It is important in antisyphilitic therapy with the arsphenamines to ensure an uninterrupted series of arsenical injections at weekly intervals over a period of at least six months except for a four-weeks rest period beginning at the end of the 10th week of treatment. As an attack of post-arsphenamine jaundice necessitates the withholding of arsenic during the period of icterus and for some weeks or months thereafter, the chances of a cure of the syphilitic infection are considerably diminished. Any treatment which would tend to reduce the incidence of post-arsphenamine jaundice, postpone it to late in the course of treatment, or, alternatively, so to reduce its severity as to enable the patient to continue to receive arsenical treatment, would be of value.

The Investigation

The experiments covered the whole of the year 1943 and the first three months of 1944. During this 15 months the post-arsphenamine jaundice occurred in the control groups in 32 out of 36 cases (61%). The time of greatest incidence of the disease in these groups was between the 14th and 19th weeks of antisyphilitic treatment, when 18 cases occurred—i.e., 82% of all cases. The control and treated groups consisted of patients who received all their antisyphilitic treatment at one clinic (M.I.H.). The experiments were designed so that protective treatment would begin just before the time of greatest incidence of the disease—i.e., at the 14th week. The numbers in each group were determined by the patients available, the quantity of the various preparations and amino-acids at our disposal, and the inevitable loss of men from the groups owing to transfer outside the area served by the clinic. It was not possible to control the diet, as all patients were serving with their units and attended the clinic only as out-patients. It was noted that there was no significant difference in the incidence of jaundice among syphilitics from different units.

The routine antisyphilitic treatment used on all the patients in the control and treated groups consisted of 4 courses, each of 10 weeks, with a rest period of 4 weeks between courses. The weekly treatment consisted of an intravenous injection of 0.6 g. neoarsphenamine and an intramuscular injection of 0.2 g. bismuth in watery suspension. The first week of antisyphilitic treatment (A.S.T.) was reckoned to be the 7 days immediately following the first injection treatment. The weeks of treatment were reckoned consecutively from the first, and included the rest periods. Thus the 15th week of treatment was the week following the first injection of the second course.

Alternate patients arriving at the 14th week of treatment were chosen as controls and given no protective treatment. The remainder were allocated to one or other experimental group. In this way a continuous series of control and experimental groups was maintained for 15 months.

At the start of the investigation we had available a small supply of a dried casein digest prepared by spray-drying a papain-trypsin digest of pure casein. Owing to its unpalatable taste the powder was administered in capsules each containing 0.5 g. of digest. It was found that the practical upper limit of dosage was 20 capsules (10 g. digest) each day. These were given in 4 doses each of 5 capsules at 4-hourly intervals. This experiment was Series I.

To increase the amount of sulphur-containing amino-acids in the daily doses of digest we reinforced the dried casein digest with cystine. As it is well known that cystine can act as a "sparer" of methionine provided the minimal daily requirements of methionine are present in the diet, we thought that the reinforced digest might be more effective than the simple digest powder. To each 97.5 g. of digest 2.5 g. of cystine was added. Assuming that each molecule of cystine in the mixture would "spare" two molecules of methionine, the "maximum effective" methionine content of a daily dose of reinforced digest of 10 g. would be approximately:

Casein digest (9.75 g.)	=	312 mg. methionine
Cystine (0.25 g.)	=	155 mg. methionine
"Maximum effective" methionine content ..		467 mg. per day

It is probable that such an estimate exceeds the actual effective methionine content, but we had no means of assessing the latter. This experiment was Series II. It was necessary to determine if cystine alone was of value, and four different experiments with different dosages and covering differing periods of administration were carried out. These form Series III. Finally, when pure methionine became available this substance

was given in doses of 0.6 g. per day. This formed the Series IV experiment.

The scheme of each of the experiments is detailed below:—

Series I: 10 g. casein digest daily during the 14th and 15th weeks of A.S.T.

Series II: 10 g. reinforced casein digest daily from the 14th to 19th weeks (inclusive) of A.S.T.

Series III A: 0.5 g. cystine from the 14th to 16th weeks (inclusive of A.S.T.

B: 1.2 g. cystine daily during the 14th to 16th weeks (inclusive) of A.S.T.

C: 0.6 g. cystine daily during the 14th to 19th weeks (inclusive) of A.S.T.

D: 1.2 g. cystine daily during the 14th week, followed by a single dose of 2.4 g. cystine at the time of arsenical injection on the 15th to 19th weeks of A.S.T.

Series IV: 0.6 g. methionine daily during the 14th to 19th weeks (inclusive) of A.S.T.

During arsenical treatment it had been observed that when some or many of the pre-icteric signs and symptoms of post-arsphenamine jaundice are present an injection of neo-arsphenamine (0.6 g.) almost invariably was followed by icterus within 7 days. When the injection is withheld most patients (80% or more) developed icterus within the same time. Biopsy findings made it clear that liver damage is usually well marked before icterus appears. For these reasons we considered that post-arsphenamine jaundice had occurred when some or all of the characteristic prodromata were present. In some patients, however, the prodromata were absent and icterus was the first sign of the disease. To avoid using the term "post-arsphenamine jaundice" when no icterus was present, we propose to use the term "liver damage" to include both icteric and non-icteric cases of post-arsphenamine jaundice. The general results are summarized in Table I.

TABLE I

Series	Total Cases	Appearance of Liver Damage (Week of A.S.T.)					Total Jaundice Cases
		14–15	16–19	20–24	25–28	29–38	
I	8	2	4	–	–	–	6
II	11	–	5	1	2	1	9
III A	6	1	3	–	–	–	4
III B	6	–	6	–	–	–	6
III C	6	1	3	–	–	1	5
III D	6	–	–	1	–	1	2
IV	10	–	1	3	1	–	5
Totals treated ..	53	4	22	5	3	3	37
Control ..	36	8	10	4	–	–	22

Explanation of Graphs.—The detailed results are expressed graphically in Figs. 1–6. The vertical bars at weekly intervals indicate the injection of neoarsphenamine; the height of the bar is proportional to the dose of arsenical given. The horizontal shaded bar shows the duration of the protective treatment, and increases in its width are proportional to the daily dose given when this was increased. The narrow horizontal black bar indicates the appearance of typical prodromal signs and symptoms. Icterus is indicated by a doubling of the width of the bar. Duration of the illness is shown by the length of the bar. The broken line in Fig. 3 indicates treatment with reinforced casein digest.

The effect of the various treatments in deferring liver damage is summarized in Table II.

TABLE II

Series No.	Total Cases	Duration of Treatment (Weeks)	Additional Sulphur in mg./day	Cases of Liver Damage	
				During Treatment	During 21 Days following Treatment
III D ..	6	6	640*	0	0
III B ..	6	3	320	0	6
III C ..	6	6	160	4	0
II ..	11	6	143	6	0
III A ..	6	3	133	1	3
IV ..	10	6	122	1	1
I ..	8	3	78	5	1

* Given as a single dose on day of injection of neoarsphenamine.

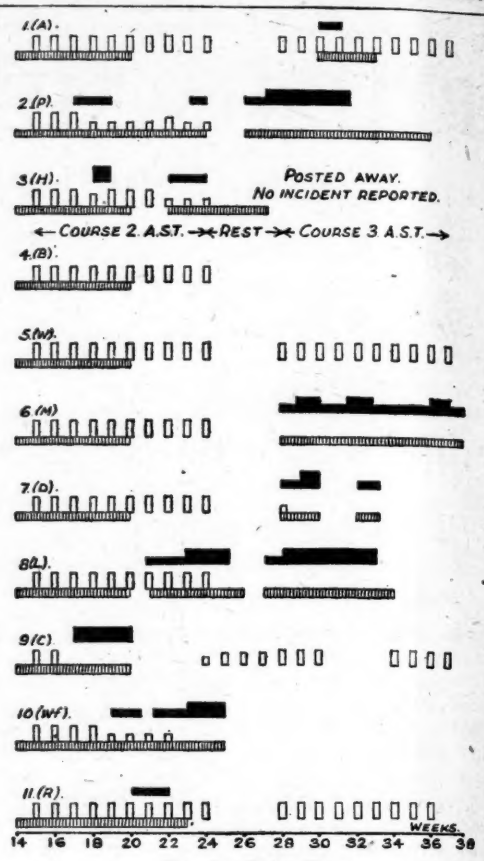

FIG. 1.—Series II.

Comment

In assaying the value of the "protective" treatments we felt we had to provide answers to the following questions:

(*a*) Is the "protective" treatment of value in reducing the incidence of liver damage during the 15th to 24th weeks of anti-syphilitic treatment (A.S.T.)?

(*b*) Is there any evidence that the "protective" treatment shifts the incidence of liver damage towards the end of the second course of A.S.T.—i.e., towards the 24th week?

(*c*) Does the "protective" treatment prevent the appearance of icterus when prodromal signs and symptoms have appeared and arsenical administration is continued?

(*d*) Is the "protective" treatment to prevent the development of icterus effective only when arsenical injections are suspended or the dose is reduced?

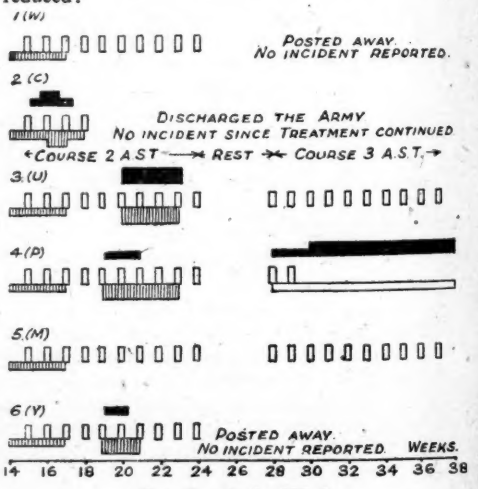

FIG. 2.—Series III A.

The immediately effective treatments are apparently those given in Series III B and D, when no sign of liver damage appeared during the period of treatment. In Series III however, all 6 patients in this group had evidence of

damage within 21 days after the cessation of preventive treatment, while no such cases appeared in Series III D. The next most effective treatments seemed to be those in Series III A and Series IV, in which only one case in each appeared during treatment. Within 21 days three cases of liver damage occurred in Series III A and one in Series IV.

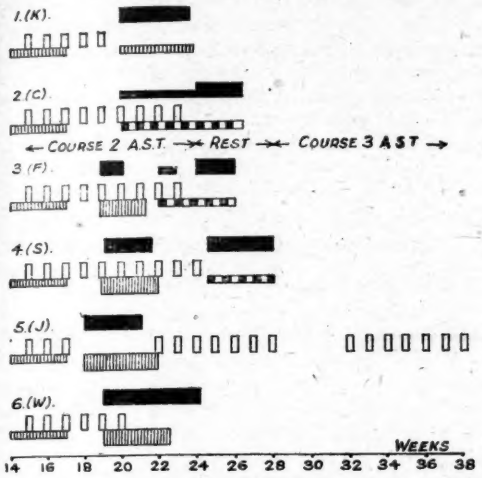

FIG. 3.—Series III B.

As the numbers in each of these groups are too small to bear statistical analysis it is not unreasonable to add them together and to compare the findings with the control group. From the control group (36 cases) the number of cases for a smaller group of 28 cases may be calculated and the probable number of cases during certain weeks predicted. Analysis of a larger control sample (150 cases) has shown that the control group is in fact a fair sample and the incidence of liver damage in the various periods is representative. The analysis is given in Table III.

TABLE III.—*Cases of Liver Damage during Weeks of A.S.T.*

	Total	14th–15th Weeks	16th–19th Weeks	20th–24th Weeks
Controls (36)	14·7	6·2	7·7	0·8
Treated groups (28), III A, B, D, and IV	15	1	10	4

In the groups where "protective" treatment was apparently effective the incidence of liver damage was not reduced during the second course of antisyphilitic treatment. This provided an answer to our first question. With regard to the second

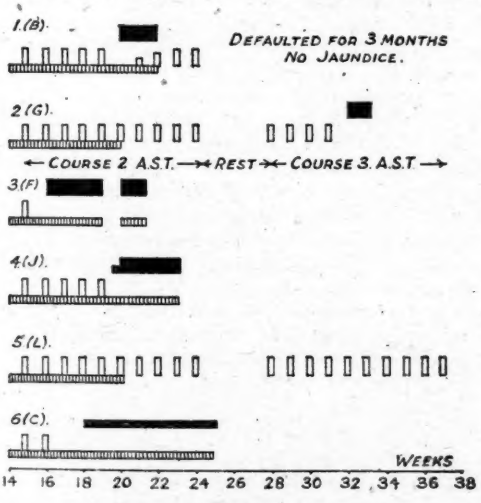

FIG. 4.—Series III C.

question, there is a tendency for more cases to appear later in the second antisyphilitic course than towards its beginning. In Series III A and B the "protective" treatment was prolonged over 3 weeks instead of over 6 weeks as in Series III D and Series IV. If this treatment had been prolonged for 6 weeks there is a possibility that the nine cases of liver damage which appeared within 21 days after the end of "protective" treatment might not have developed until the 20th–24th week period. In such an event the shift might have been more pronounced. Series III A and C are, however,

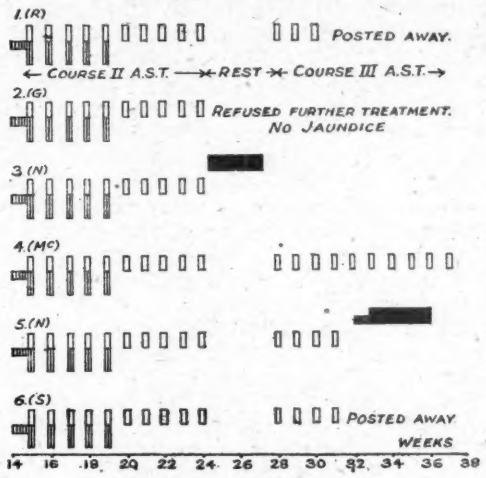

FIG. 5.—Series III D.

practically identical in daily dosage of cystine (0.5 and 0.6 g.), but differ in the length of time over which the cystine was given. Reference to Figs. 2 and 4 shows that within the first 6 weeks of the beginning of the second course of arsenical treatment each of these groups had the same number of cases of liver damage. The prolongation of treatment at the same dosage for 6 weeks apparently in no way influenced the development of liver damage in Series III C. It is a fair deduction, therefore, that such a dosage of cystine is ineffective.

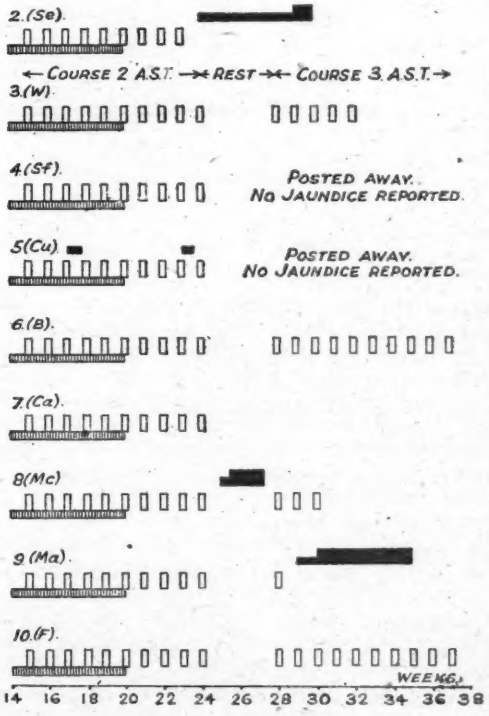

FIG. 6.—Series IV.

Doubling the daily dose of cystine for a period of three weeks (Series III B) produced no cases while treatment was being given, but all the group had liver damage before the end of the sixth week from the start of the 21-day treatment.

This experiment is inconclusive in view of what has been said above regarding Series III A and C. It is possible that if treatment had been prolonged for 6 weeks a similar result to that recorded in Series III C might have been obtained; on the other hand, it is equally possible that no cases might have occurred.

Series III D treatment, in which a daily dose of 1.2 g. cystine was given during the 14th week and was followed by single doses of 2.4 g. cystine on the days on which arsenical injections were given (15th–20th weeks), was apparently effective, as no cases of liver damage appeared either during the period of "protective" treatment or during the subsequent 21 days.

Series IV seemed to show that small doses of methionine (0.6 g.) were almost as effective as the massive doses of cystine of Series III D. It should be noted that, in spite of continued full doses of arsenic, icterus did not develop in the single case of liver damage during "protective" treatment. The very significant delay in the appearance of liver damage in the remaining four cases is noteworthy.

Series I represents an attempt to increase the daily intake of methionine by using a casein digest. The results demonstrate clearly that an extra 0.3 g. of methionine present in the daily dose of digest for 14 days had no effect on the incidence or time of appearance of the post-arsphenamine jaundice. The Series II experiments, in which cystine was added to the digest, present some interesting features. During the period up to the end of the 24th week 5 patients of the 11 treated remained free from liver damage. One (R.) showed signs of liver damage at the beginning of the 20th week, but with continued "protective" treatment did not develop icterus, although full doses of arsenic were given. Two with prodromal signs and symptoms were treated by reducing the arsenical dosage and continuing the "protective" treatment. One of these (P.) did not become icteric, but a full dose of arsenic produced a reappearance of the prodromal phenomena. The other (Wf.), in spite of reduced dosage, eventually became icteric. A mild icterus in one patient (H.) was treated by reducing the arsenical dosage. At the end of 7 days icterus had disappeared and full arsenical treatment was resumed. The suspension of "protective" treatment for two weeks induced a reappearance of prodromal signs and symptoms. One patient (L.) showed no sign of liver damage until one week after the end of the protective period. Resumption of "protective" treatment, with full doses of neoarsphenamine, however, did not prevent the appearance of jaundice. He relapsed again after being without "protective" treatment for one week. Arsenic was not given during the relapse. Icterus appeared in one patient (C.) after two arsenical injections. Suspension of injections and continuation of the "protective" treatment were followed by disappearance of icterus in 3 weeks. Resumption of arsenical injections later without "protective" treatment provoked no relapse.

These results suggest that the addition of but a small quantity of cystine to the casein digest is just sufficient to protect some individuals from developing liver damage, others from the development of icterus, others also from icterus but only if the arsenical dosage is reduced; and others are not so protected. This scheme of "protective" treatment seems therefore to represent almost the balance between adequate and inadequate treatment. Assuming that the addition of 0.25 g. cystine acted by sparing methionine, it would represent the sparing of not more than 0.16 g. The total "effective" methionine supplement would therefore probably not exceed 0.4 g. per day.

Two possible explanations of these results must be considered. The protective compounds might be effective in rendering the neoarsphenamine non-toxic to the liver and presumably also to the spirochaete. Possibly post-arsphenamine jaundice is a partial deficiency disease in the sense that certain compounds, which enable the liver successfully to resist the toxic effects of virus infection combined with neoarsphenamine injections, are not present in optimal quantities in the wartime diet. Supplementation with these compounds presumably may be effective in altering the incidence, time of onset, or severity of the liver damage when it occurred.

Voegtlin (1925) showed that neoarsphenamine in the concentration found in the blood during antisyphilitic treatment was not lethal to the spirochaete until it had been oxidized to arsenoxide. Arsenoxide is rendered non-lethal, however, if it is allowed to combine with a sulphydryl-containing compound such as cysteine. Eagle (1939) suggested that arsenoxide killed the spirochaete by combining with sulphydryl groups concerned in the respiration of the cell. Glutathione is one such compound. The probability is that arsenoxide is toxic to the liver cell through a similar mechanism. It is conceivable that cystine (being readily convertible to cysteine in the liver) might be utilized in this way to detoxicate the arsenoxide. In two of the cystine-protected series the times during which "protective" treatment was continued were identical. In Series III C, however, the cystine was given daily in doses of 0.6 g./day or 4.2 g./week, whereas in III D, with the exception of the first week, the cystine was all given on the same day as the arsenical injections in a dose four times the daily dose of III C but only slightly more than half the total weekly dose. In both groups the overall incidence of liver damage was unaffected. In III C the cases occurred at the usual time or were only slightly delayed. In III D the cases were very significantly delayed in onset (Fig. 5). Such a contrasting result can best be explained by assuming that cystine given in mass doses on the day of the arsenical injection is mainly effective by acting as a chemical detoxicating agent for the arsenoxide, thus relieving the liver from the effects of arsenoxide for at least six weeks and enabling it to deal with later arsenical injections successfully for a limited period. There is only one other series in which the occurrence of liver damage was delayed to a comparable extent. In Series IV methionine was given in a manner corresponding exactly to Series III A, discussed above, but the results obtained were strictly comparable to those in III D. It seems impossible that methionine in this case could be acting as a direct detoxicating agent at a level of dosage where cystine was ineffectual. It therefore becomes necessary to assume that methionine, unlike cystine in large doses, is effective in the second of the two ways suggested above.

It must be made quite clear that Eagle's work was done *in vitro* and may therefore not be valid under *in vivo* conditions. The experimental evidence on animals is at present equivocal. In some measure this may be due to dietary variations which Martin and Thompson (1943) showed could introduce variations in the acute toxic effects of arsphenamine as great as 50%. The consensus of opinion, however, is that the sulphydryl compounds, such as cysteine, can diminish the toxic effects of the trivalent organic arsenicals—neoarsphenamine and arsenoxide. Cystine apparently can only exert such an action when it is reduced to cysteine. This reduction of cystine to cysteine can occur in the liver.

The conclusion that cystine is mainly effective as a detoxicating agent, whereas methionine remedies a specific dietary deficiency, is strengthened when actual diet figures of these men are considered. The British Army Home Forces daily ration as issued contains 118 g. protein, of which 58% is of vegetable origin. In fact, we found that the maximum these men appeared to be eating was 100 g. of protein per day. This would give a sulphur intake of about 0.96 g. daily, representing about 2 g. each of methionine and cystine. It is well known that the borderline between adequate and inadequate quantities of the various essential food constituents may be narrow. If there is a suboptimal methionine intake in these men receiving arsenical treatment an increase of 25% might easily be sufficient to raise it to an effective level. On the other hand, the quantities of a sulphydryl-containing compound sufficient to protect the liver by direct detoxication of the arsenic would have to be very much larger. One molecule of neoarsphenamine requires four sulphydryl groups for detoxication. If all the administered cystine were converted directly to cysteine and all this cysteine were then combined with arsenoxide, the weekly dose of 0.6 g. neoarsphenamine would require 0.6 g. cystine. This would need to be available during the 24 hours following the injection, as it is known that the greater part of the spirochaeticidal action of neoarsphenamine, which we assume to be similar to its hepatoxic action, occurs within this period. In view of the many ways in which cystine can be metabolized, apart from its conversion to cysteine, it is not surprising that the minimal effective dose of cystine should approach 2.4 g. when given

on the actual day of injection, or that larger quantities spread over a longer period should be relatively ineffective.

The metabolism of methionine and cystine cannot, however, be regarded as unrelated to each other. Part of the methionine in the diet is undoubtedly converted in the body to cystine and its derivatives. It is probable, therefore, that an increased daily cystine intake given to an individual with a suboptimal methionine intake would increase the amount of methionine available for those functions which cystine itself cannot perform. Such a methionine-sparing effect of dietary cystine was found to occur in growing rats by Rose *et al.* (1937). It is likely that the definite results obtained with daily doses of cystine at the lower levels (Series III A, B, C) and when it was added to the casein digest (Series II) are due to this effect.

Such theoretical discussions, however, would be better based on larger series of cases. At present it is not possible to extend this series, but the fact is clear that adequate protection in the second arsenical course can be attained. Practically it would seem desirable that men under this treatment should receive at least 2.5 g. methionine daily, and preferably 3 g. This could be done if their diet were supplemented either with the synthetic compound or with about a pint of milk daily. The use of synthetic cystine in quantities sufficient to produce the required result is not desirable, as the effect of cystine may be to detoxicate the arsenic and thus render ineffectual the antisyphilitic treatment. Moreover, we have found suggestions in some of our cases that the effect of cystine on established liver damage may be conducive to cirrhosis.

Summary

An attempt has been made to control the occurrence of liver damage in syphilitics under treatment with neoarsphenamine.

Sulphur-containing amino-acids were given during that period of treatment when the expected incidence of liver damage was maximal.

Four preparations were tested—casein digest, casein digest reinforced with cystine, cystine, and methionine.

These preparations had no effect on the overall incidence of liver damage. Certain of them, however, were markedly effective in (*a*) shifting the time of peak incidence of liver damage towards the end of the second course of antisyphilitic treatment or later; (*b*) moderating the severity of the liver damage when this did occur.

The effect of casein digest reinforced with cystine was less than that of an equivalent quantity of synthetic methionine.

Cystine produced an effect similar to that of methionine only when given in large quantity on the day of the arsenical injection.

It was concluded that men undergoing antisyphilitic treatment should receive dietary supplements as a prophylactic measure against jaundice.

These supplements should not take the form of large quantities of cystine, as this may reduce the chances of the antisyphilitic treatment being successful.

We wish to thank Brig. T. E. Osmond for putting at our disposal the facilities for carrying out this work and for his interest and encouragement. The pure amino-acids used in these experiments were presented by friends in Canada and the United States. We are grateful to them for their generous gifts. The casein digests were prepared by Mr. J. I. M. Jones of British Colloids Ltd. To him and his directors we express our thanks for their co-operation and interest, and for gifts of ample supplies of material.

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A Tsetse Fly and Trypanosomiasis Committee has been appointed by the Secretary of State for the Colonies to consider and advise on the co-ordination of action, including research, directed against human and animal trypanosomiasis, and in particular against the tsetse fly. The Dominions Office and the Sudan Government are represented on the committee, whose chairman is Mr. G. H. Creasy, of the Colonial Office. The members include Prof. P. A. Buxton, London School of Hygiene and Tropical Medicine; Dr. H. Lyndhurst Duke, lately director of the Human Trypanosomiasis Institute in Uganda, and chairman of the League of Nations Sleeping Sickness Committee; Prof. I. M. Heilbron, Imperial College of Science; Dr. E. M. Lourie, Liverpool School of Tropical Medicine; Sir Guy Marshall; Dr. S. A. Neave, director of the Imperial Institute of Entomology; and Dr. A. G. H. Smart, Medical Adviser to the Secretary of State for the Colonies.

ACUTE PERFORATED PEPTIC ULCER

FREQUENCY AND INCIDENCE IN THE WEST OF SCOTLAND*

BY

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AND

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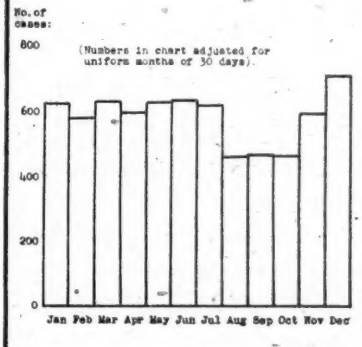
Case Frequency by Months (3 Main Hospitals; 20-year Period)

Cases occurring in like months over the 20-year period were added together. Fig. 9 shows the monthly distribution so obtained, and demonstrates the divergence between the number of perforations observed and the number which might have been expected if the distribution were uniform (due allowance being made for the number of days in the various months). It will be seen that perforations are unduly common in

Fig. 9. PERFORATED PEPTIC ULCER

CASE FREQUENCY BY MONTHS, COMPARED WITH UNIFORM DISTRIBUTION. 1924-1943

(Both Sexes)



Month	Perforations observed	Perforations "expected"	Observed minus "expected"
Jan.	653	607.3	+45.7
Feb.	537	555.3	-16.3
Mar.	658	607.3	+50.7
Apr	600	587.9	+12.1
May	655	607.3	+47.7
June	640	587.9	+52.1
July	647	607.3	+39.7
Aug.	478	607.3	-129.3
Sep.	470	587.9	-117.9
Oct.	479	607.3	-128.3
Nov.	597	587.9	+9.1
Dec.	742	607.3	+134.7
Total	7156	7156.0	0

$X^2 = 128.5$ P is remotely small

December and relatively uncommon in August, September, and October. This distribution obtained fairly consistently throughout the 20-year period. It is highly improbable that such wide departures from uniformity have arisen by chance.

There is no obvious explanation of the December rise, which is distributed throughout that month and not related to the Christmas season. The low incidence in summer may possibly have a nutritional basis or may be related to the holiday season. In this connexion it is relevant to state that in the West of Scotland July is the popular holiday month, and it will be seen that the July incidence is not low; but it is possible that the period of rest at that time confers a measure of protection during the ensuing months.

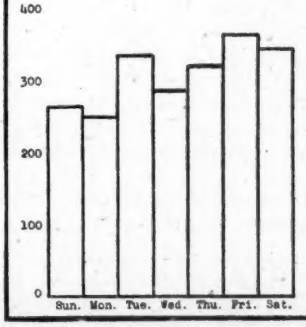
Incidence by Days of Week (2 Hospitals; 6-year Period)

The incidence of perforation by days of the week in two hospitals (Royal and Western Infirmaries) was determined for the years 1938–43. Cases occurring on like days were added together, and the result is given in Fig. 10. It will be seen

Fig. 10. PERFORATED PEPTIC ULCER

Incidence by Days of the Week, compared with uniform distribution

(1938-1943)



Day	Perforations observed	Perforations "expected"	Observed minus "expected"
Sun.	271	314.6	-43.6
Mon.	255	314.6	-59.6
Tues.	340	314.6	+25.4
Wed.	290	314.6	-24.6
Thurs.	326	314.6	+11.4
Frid.	369	314.6	+54.4
Sat.	351	314.6	+36.4
	2202	2202.2	

$X^2 = 35.31$
P very much less than 0.01

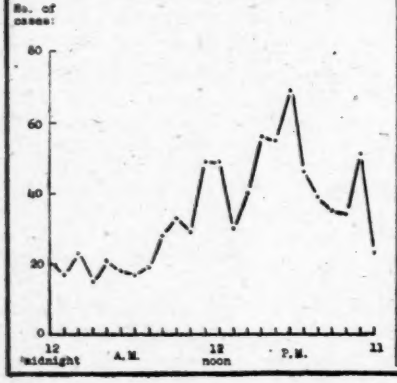
* A survey made under the auspices of the Nuffield Provincial Hospitals Trust. Concluded from page 620.

that the incidence was lower on Sundays and Mondays than on other days. It is hardly necessary to state that the departure from uniformity cannot be accounted for by treatment being withheld at the week-end. It is, moreover, too great to be readily attributed to chance. The suggestion is offered that the deficiency of perforations on Sunday and Monday may be due to rest at the week-end.

Incidence by Hours of the Day

Perforation of a peptic ulcer occurs with such dramatic suddenness and is marked by such intense pain that it is generally possible to determine the precise time of onset. In 951 perforations occurring in 884 patients treated at the Western Infirmary during 1938–43 the time of perforation was recorded in 816 (Fig. 10A). It will be noted that few perforations occur

Fig. 10A. Hour of Perforation



Hour of Perforation	No. of Cases
Midnight – 1 a.m.	20
1 a.m. – 2 a.m.	17
2 a.m. – 3 a.m.	23
3 a.m. – 4 a.m.	15
4 a.m. – 5 a.m.	21
5 a.m. – 6 a.m.	18
6 a.m. – 7 a.m.	17
7 a.m. – 8 a.m.	19
8 a.m. – 9 a.m.	28
9 a.m. – 10 a.m.	33
10 a.m. – 11 a.m.	29
11 a.m. – 12 noon	49
12 noon – 1 p.m.	49
1 p.m. – 2 p.m.	30
2 p.m. – 3 p.m.	40
3 p.m. – 4 p.m.	56
4 p.m. – 5 p.m.	55
5 p.m. – 6 p.m.	69
6 p.m. – 7 p.m.	46
7 p.m. – 8 p.m.	39
8 p.m. – 9 p.m.	39
9 p.m. – 10 p.m.	34
10 p.m. – 11 p.m.	51
11 p.m. – Midnight	23
Not stated	135
Total	951

during the night, and that during the day the incidence gradually rises to a maximum in the period 3 p.m. to 6 p.m., thereafter falling gradually. It is relevant to state that the usual meal-times of the working population in Glasgow are: breakfast 7 to 7.30 a.m., lunch 12 noon, supper 5.30 to 6.30 p.m. The incidence of perforations in relation to meal-times is not clear and demands further study. It is noteworthy that the incidence is highest towards the end of the working day and lowest during the period of rest. This may be compared with the low incidence at the week-end and after the summer holiday period.

Incidence by Site of Ulcer

At two of the main Glasgow hospitals (Western and Victoria Infirmaries) we have classified perforations treated during the period 1924–43 according to the site of the ulcer. The classification has been made on the basis of operation notes recorded in the clinical case-sheets. In Glasgow it is the usual practice that operation notes are written (or dictated) in full by the surgeon responsible, and the records are generally detailed and precise. Consequently we have been able to establish the situation of the ulcer in 97% of cases.

The main difficulty has been in regard to ulcers situated at or close to the pylorus. In an emergency operation if the anatomical landmarks are obscured by inflammation or adhesions it is impossible to determine the precise site of such an ulcer with certainty. As a result, in some cases (a small minority) the ulcer has been recorded as being situated "at the pylorus" or "close to the pylorus" with no more exact guide to its site of origin. Since these juxtapyloric ulcers are closely akin to duodenal ulcers in appearance and behaviour (and very different from the typical lesser-curve gastric ulcer) we have grouped them with duodenal ulcers under the title "pyloro-duodenal." As their number is small (about 5% of the total) our conclusions on the relative incidence of gastric and duodenal ulcer are not affected materially by this arrangement.

It will be seen (Table II) that duodenal ulcer far exceeded all other types, accounting for 82.95% of the total. The proportion of duodenal to gastric ulcer is about 13 to 2. Perforated anastomotic ulcers numbered 52, or 1.34% of the total—a remarkably high incidence considering that even in the heyday of gastro-enterostomy the proportion of all ulcer patients subjected to this type of operation must have been very small.

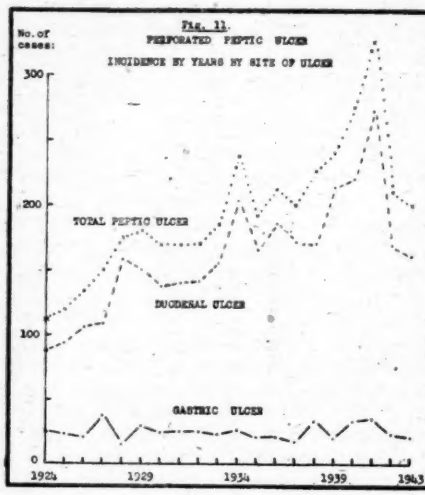
TABLE II.—*Perforated Ulcer: Incidence by Sites, 1924–43*

Total	Gastric	Pyloro-duodenal	Anastomotic	Site not Stated
3,882	493 (12·70%)	3,220 (82·95%)	52 (1·34%)	117 (3·01%)

Perforated Gastric and Duodenal Ulcer: Incidence by Years (2 Hospitals; 20 Years)

Fig. 11 shows the incidence by years of gastric and duodenal perforations separately and, for comparison, the incidence by

Fig. 11.



Year	Total	Gastric	Duodenal
1924	112	25	87
1925	118	25	93
1926	132	20	112
1927	151	37	113
1928	176	16	157
1929	181	29	150
1930	169	24	138
1931	168	25	140
1932	171	25	141
1933	187	23	156
1934	237	26	203
1935	192	20	166
1936	213	21	185
1937	200	17	170
1938	226	33	171
1939	241	19	213
1940	274	32	220
1941	325	36	273
1942	211	22	169
1943	198	20	161
Total	3882	493	3320

years of all types of perforation together. It will be seen that the incidence of gastric perforation was not materially changed during the 20-year period, whereas the incidence of duodenal perforation has altered greatly. Indeed, the changing incidence of perforated ulcer as a whole merely reflects the growth of its duodenal component.

Site Incidence by Sex (2 Hospitals; 20 Years)

Table III shows the incidence in males and females of ulcers at different sites. It will be seen that males predominate in perforations of all types. The sex difference is particularly striking in anastomatic ulcers, all of which occurred in males.

TABLE III.—*Site Incidence by Sex*

Site	Male	Female
Gastric	442 (12·02%)	51 (25·00%)
Duodenal	3,076 (83·63%)	144 (70·59%)
Anastomotic	52 (1·41%)	0 —
Site not stated	108 (2·94%)	9 (4·41%)
All sites	3,678 (100·00%)	204 (100·00%)

It will be noted that there is a difference in the sex ratio of gastric and duodenal perforation. In males 12% of perforations were gastric while 83.6% were duodenal; the comparable figures for females were 25% and 70.6%. Statistical analysis shows that it is highly improbable that the difference in sex ratio has arisen through the play of chance.

Fatality from Perforated Peptic Ulcer

The fatality from perforated peptic ulcer is influenced, as we shall show, by many factors—the sex and age of the patient, the site of the ulcer, the season (winter or summer), the promptness of treatment, as well as (doubtless) the skill of the surgeon and the nature of the operative technique. Perhaps also there may be differences based on geography and race and nutritional standards.

We feel it necessary to emphasize the importance of these factors, for they have an obvious bearing when comparing the mortality rates given by different workers. Unfortunately, few reports in the past have provided the data necessary to make such a comparison with much confidence. For this

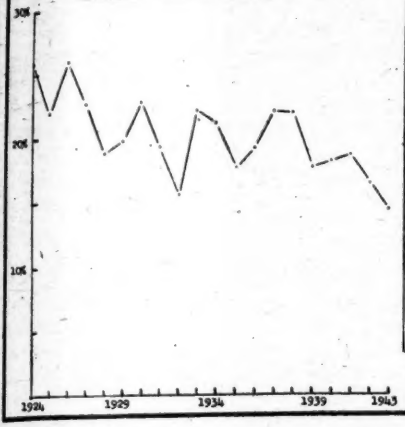
reason we make no attempt to compare the results reported here with those of other workers.

In the 7,156 perforated peptic ulcers contained in our 20-year series the deaths numbered 1,396,* or 19.5%. During the 20 years the fatality rate has fallen from 25.7% in 1924 to 14.1% in 1943 (see Fig. 12). The fall has not been a steady

Fig. 12.

PERFORATED PEPTIC ULCER

PERCENTAGE FATALITY, 1924-43



Year	No. of cases	Recovered	Died
1924	191	142	49
1925	205	160	45
1926	274	203	71
1927	283	222	61
1928	318	258	60
1929	335	269	66
1930	311	240	71
1931	328	265	63
1932	336	284	52
1933	317	247	70
1934	395	312	83
1935	378	312	66
1936	373	302	71
1937	374	293	81
1938	431	338	93
1939	432	357	75
1940	518	425	93
1941	615	502	113
1942	366	306	60
1943	376	323	53

χ^2 = 37.11 n = 19
P = less than .01

one, but the trend as a whole is quite clear, and statistical analysis shows that it is unlikely to have occurred as a result of chance. It should be noted that this improvement has been achieved despite an increase in the age incidence. Probably it is attributable mainly to increasing promptness of treatment.

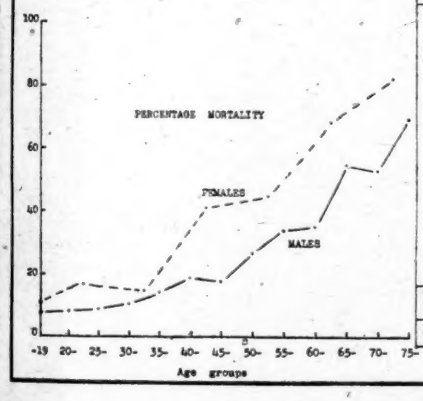
It is relevant to state at this point that in over 90% of cases in our series the operative treatment has consisted in simple closure of the perforation, without gastro-enterostomy. Primary gastrectomy is not practised.

Deaths by Age Groups in Males and Females (3 Hospitals; 20 Years)

Fig 13 shows the fatality rate in males and females at various age groups. Males have been taken in 5-year groups; females, owing to the smaller numbers, in 10-year groups.

Fig. 13. PERFORATED PEPTIC ULCER

Deaths % DEATHS BY AGE GROUPS



Age Group (yrs)	MALES No. of cases	MALES Deaths	FEMALES No. of cases	FEMALES Deaths
-19	270	21	19	2
20-	544	44	48	8
25-	768	65		
30-	945	97	76	11
35-	951	134		
40-	814	150	96	40
45-	723	128		
50-	661	176	61	28
55-	454	155		
60-	361	126	47	32
65-	184	101		
70-	77	41	11	9
75-	36	25		
Not stated	8	2	2	1
TOTAL	6796	1265	360	131

It will be seen that the fatality rate increases with age and that in all age groups the fatality rate in females exceeds that in males. Over the whole series the fatality rate for males is 18.6%, for females 36.4%. In males the fatality rate remains below 10% until the age of 30 and below 20% until the age of 50, after which it rises rapidly. In females the rise occurs earlier and is more pronounced. The higher fatality rate in females is not due to the larger proportion of gastric ulcers occurring in that sex, nor do our records indicate that it is due to any difference in the promptness with which treatment is instituted.

Deaths by Season (3 Hospitals; 20 Years)

Table IV gives the deaths for the winter and summer months. It will be seen that the rate is considerably higher in winter than in summer. Statistical analysis shows that the difference

TABLE IV.—*Perforated Peptic Ulcer. Deaths by Season (Both Sexes)*

	No. of Cases	Recovered	Died
Winter (Oct.–March) ..	3,666	2,901	765 (20·9%)
Summer (April–Sept.) ..	3,490	2,859	631 (16·4%)
Total	7,156	5,760	1,396 (19·5%)

χ^2 = 8·907. n = 1. P = less than 0·01.

is unlikely to have occurred by chance. Nor do our records provide evidence that the disparity can be accounted for by seasonal variations in the age incidence or sex incidence or in promptness of treatment. It may well be attributable to the increased risk of pulmonary complications in the winter months.

Deaths by Site of Ulcer (2 Hospitals; 20 Years)

In males the fatality rate for perforated gastric ulcer is much higher than for duodenal, and the difference is far more than can be accounted for by differences in the age incidence.

TABLE V.—*Deaths by Site of Ulcer*

Site	Males			Females		
	Recovered (No.)	Died		Recovered (No.)	Died	
		No.	%		No.	%
Gastric ..	316	216	28·5	32	19	37·3
Duodenal ..	2,625	451	14·6	106	38	26·4
	χ^2 = 8·907 P = much less than 0·01			χ^2 = 2·042 P = *c.* 0·18		

In females also the fatality rate is higher in gastric than in duodenal perforation, though, perhaps owing to the fewness of cases, the difference is not statistically significant. Thus perforated gastric ulcer is a more dangerous disease than perforated duodenal ulcer. Our records give no indication that this is due to the promptness with which the two types are submitted to treatment. It may well be due to the fact that in gastric ulcer the perforation is generally of larger size and permits greater escape of more heavily infected contents.

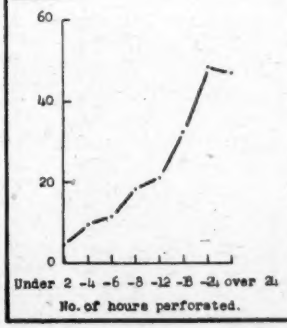
Deaths by Delay in Treatment (1 Hospital; 6 Years)

In 939 perforations occurring in 872 patients admitted to one hospital (Western Infirmary) during the period 1938–43 the fatality rate has been assessed by the delay in treatment. In 813 of these cases the number of hours between the time of perforation and operation was recorded. The time interval

Fig. 14. Perforated Peptic Ulcer.

Deaths by Delay in Treatment.

Deaths %



Hours Perforated	No. of Cases	Deaths
Under 2	90	4
2–4	261	25
4–6	197	23
6–8	103	19
8–12	76	16
12–18	40	13
18–24	31	15
Over 24	15	7
Not stated	126	23
Total	939	145

* This figure and those given elsewhere throughout the report include all deaths occurring at any period after perforation while in hospital. It is relevant to state also that our series includes cases admitted moribund and not subjected to operation; it excludes cases diagnosed as "leaking ulcer" but recovering without operation.

ranged from half an hour to 3 days. It will be seen that in a large majority of cases operation was performed within 6 hours of perforation. This promptness of treatment is doubtless due partly to the fact that the area served is predominantly urban, but much credit must also be given to the diagnostic acumen of the practitioners in this area. Fig. 14 shows that in this series the fatality rate rose progressively with delay in treatment. This, of course, confirms general experience and the reports of all previous observers.

Summary

Figures are reported relating to the incidence of perforated peptic ulcer in an area in the West of Scotland with a population of over 2 millions. The more notable findings are as follows:

1. From 1924 to 1938 there was a progressive increase in the incidence of perforations. During the war the steady increase has been interrupted by a marked rise in 1940–1, followed by a return to a lower level. These changes almost entirely concern duodenal ulcer.

2. The 1940–1 rise was not correlated with air raids in this part of the country. It is suggested that, in addition to anxiety about the war situation, overwork and perhaps undernutrition may have exerted an influence.

3. The sex ratio has undergone little change during the 20-year period. The rise in 1940–1 and the fall in 1942–3 were confined to men. In women during the war years the general pre-war trend was maintained. This finding is somewhat surprising in view of the great changes which have taken place since 1939 in the habits and working conditions of women.

4. Perforation is rare in childhood; its incidence rises rapidly in adolescence and attains a maximum between the ages of 30 and 40 years. Since 1924 there has been a rise in the mean age which does not appear to be due entirely to ageing of the population. The mean age is higher in females than in males.

5. Perforations are unduly common in December and relatively uncommon in August, September, and October. This low incidence in the summer months may possibly have a nutritional basis or may be related to the holiday season.

6. Perforations are less frequent on Sundays and Mondays than on other days. This may perhaps be related to rest at the week-end.

7. Perforations are unduly common between 3 p.m. and 6 p.m. and comparatively uncommon during the night and morning. The relation of these phases to meal-times is not clear and requires further study. There may be a correlation with periods of stress and rest respectively.

8. The fatality rate from perforations increases with age and with delay in treatment. It is greater in gastric than in duodenal ulcer, in females than in males, in winter than in summer.

This survey has been carried out under the auspices of a committee of the Nuffield Provincial Hospitals Trust appointed in Glasgow for the study of sickness records. Thanks are due to our surgical colleagues and the hospital authorities for furnishing us with the information on which this survey is based, and particularly to the medical superintendents of the three main voluntary hospitals, who have given us every facility for extracting the hospital records. Our task has been greatly lightened by the generous help we have received on all sides. We acknowledge also our debt to Prof. J. W. McNee, of whose staff one of us is a member.

Extracting clinical records often proves disappointing, but in this instance we have been gratified at the amount and the detailed character of the information available, and we have pleasure in recording our appreciation of the care devoted by our colleagues, year in and year out, to this routine task of hospital work.

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That there is a real demand for a contributory hospital scheme for those who desire treatment in hospital private wards and nursing homes is shown by the progress made by the Hospital Service Plan under the chairmanship of Sir Bernard Docker and sponsored by King Edward's Hospital Fund for London. This plan has grown steadily since its inception barely two years ago, and the secretary of the London Association for Hospital Services (10, Old Jewry, E.C.2) now announces that the maintenance refund rate is to be increased from £6 a week to £6 6s., thus indicating a desire among the higher-salaried public to make provision for their dependants and themselves in the event of serious illness. The increased refund is payable to subscribers admitted to hospitals after the end of October.

EXPERIENCES WITH THE GIANT MAGNET AND METALLIC INTRAOCULAR FOREIGN BODIES IN RECENT BATTLE CASUALTIES

BY

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AND

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It is perhaps important to publish the following case just now, and we do so at the suggestion of Brig. Sir Stewart Duke-Elder.

Case History

On July 15, 1944, L/Cpl. E., a land-mine battle casualty from Normandy, was admitted to No. 4 Canadian General Hospital. He had been blown up on July 3, and was "pulseless" when picked up and transfused that evening. From toes to vertex he was spattered with wounds of various sizes. All were superficial except one in the abdominal wall, one of the left hand, and a penetrating injury of the left eyeball.

The first two wounds were operated upon in France. When received at No. 4 Canadian General Hospital the patient was in good condition. He had received intramuscular penicillin, 50,000 units five-hourly, starting on July 8, to a total of 500,000 units; it was then stopped. On the 18th it was given again—15,000 units every three hours to a total of 150,000 units.

H. A. G. D. located a small foreign body impacted in the retina about 3 d.d. down and in from the disk. The entrance wound was minute, near the limbus towards 9 o'clock. There was haemorrhage of the retina near the track of the missile, but lens and vitreous were clear. The vision was 20/20. A radiograph showed a single minute opacity corresponding in position to the visible F.B. H. A. G. D. had the case transferred to the S.E.C. Ophthalmic Centre for extraction, since his magnet was not very powerful, and assisted at the subsequent surgical procedures.

On July 15 operation was performed under novocain infiltration. Good rotation was ensured by dividing the mesial rectus. A 3-mm. incision was made in the sclera through a linear diathermy coagulation, between points of fine silk suture. The incision was seen to be about 1 mm. from the F.B., which was partially hidden by coagulum. Six short applications of the giant magnet with the tip of a beak-shaped terminal on the wound produced no movement. It was considered inadvisable at this time to extract the particle with forceps, for several reasons which need not be discussed here. The patient was retained for further consideration.

The next day, when we were dealing with a minute metallic F.B. in the vitreous of a German prisoner of war by the posterior route, Major H. W. Applin, who was collaborating, observed a slight rocking of the F.B. at the end of about the tenth short application, as the current went on and off. Thereafter the particle made larger excursions from the centre of the vitreous towards the wound and was delivered through the choroid (which had not been incised) at the thirty-fifth application. The immediate post-operative progress in this case was uneventful; the eye remained quiet, the vitreous clear, and the vision 6/6.

This experience encouraged us to continue with magnet extraction in the case of L/Cpl. E., since, meantime, some metallic particles collected from scabs on his legs had proved magnetic, and had given a positive Prussian-blue reaction when dissolved in nitric acid. On July 28 the sclera was exposed down to the previous wound and the curved terminal placed against it towards the side away from the F.B. The magnet was then used in short bursts of about 4 seconds (on a few occasions as long as 15 seconds) for 75 applications. The current was probably flowing for not more than a total of 10 minutes. During this time the F.B. was observed to rock in its bed of coagulum, gradually come out of it, and lie across the wound. The magnet was then too hot to manipulate, and it was considered that its insulation was in danger. The patient was returned to bed.

On Aug. 2, under continuous pentothal, the mesial sclera was freely exposed, the internal rectus being divided again to give free access. The scleral suture was removed from the original wound, on which the beak-shaped terminal was placed. The wound elevated slightly at the first magnet application, and the particle, less in size than the head of a half-inch pin, came out at the sixth trial without any haemorrhage or vitreous showing.

The post-operative course has been uneventful. The vitreous remained clear and the vision good—6/9 with lens.

Commentary

It has long been known that intermittent applications repeated at a number of sittings will succeed in moving a feebly magnetic particle (see Crawford, R. A. D., *Brit. J. Ophth.*, 1943, **27**, 227), and no doubt others have had similar experiences to ours with recent battle casualties; but it seemed to us and to Major Applin that it may not be generally realized that a small magnetic F.B. or a larger feebly magnetic particle may behave as a non-metallic F.B. for a considerable number of magnet applications and be labelled as such. Moreover, with such particles the magnet test of pain production in a cocainized eye is useless.

There are further lessons to be learned from this case and other recent cases we have dealt with.

1. The posterior route is ordinarily best for posterior-segment F.B.s.

2. The shortest route to the exterior is probably always best, provided it does not drag the particle over or through an intraocular part or structure of relatively greater importance than that in which it is lodged.

3. A beak-shaped magnet terminal is almost essential for work well behind the equator; a blunt cone-shaped terminal is sometimes a danger, especially with highly magnetic large bodies, unless they are situated in the anterior segment, since the field is too diffuse to direct the delivery accurately.

4. The removal of small metallic intraocular F.B.s of feeble magnetism, which it is desirable to remove as in the case of iron compounds, is sometimes determined by the patience and perseverance of operator and patient and the life of the magnet and rectifier—possibly oftener than we have thought heretofore.

5. It is perhaps stating the obvious to say that exploration of intraocular F.B.s lodged superficially in the skin of face or body or in the conjunctiva, as to their composition and magnetism, is desirable.

6. To those accustomed to the localization of civil hospitals in peacetime the slower and less accurate methods necessitated by war conditions constitute a great handicap.

7. The fact that frequent applications of the giant magnet increase the magnetism of feebly magnetic alloys should influence technique.

8. The application of a surface diathermy terminal to the sclera in the neighbourhood of a metallic intraocular F.B. is likely to produce an uncontrollable reaction emanating from the F.B. For this and other reasons (e.g., the greater difficulty of withdrawing a magnetic particle from a bed of coagulum) it is probably better technique to apply diathermy to the neighbourhood of the scleral wound after the F.B. is removed.

9. If prolonged applications of the Army portable giant magnet are required, as in the case described above, it is almost essential to place it on an adjustable stand with a tilting top, beside the operating-table.

LATENT MASTOIDITIS IN INFANCY

BY

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AND

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The frequency with which pus is found at necropsy in the middle ears and mastoid cavities of infants is now generally recognized, but the exact part it plays in the causation of death is still controversial. The present paper is based on an analysis of 120 consecutive necropsies in which the middle ears were specially examined. It is felt that observations on a comparatively small series might be of value in reaching a solution to what is admittedly a difficult clinico-pathological problem.

The Literature

The literature is extensive, but the conclusions reached by the various authors on the significance of latent mastoiditis in infancy and early childhood are by no means unanimous. In this article only a representative few of these papers will be considered. Prof. Tröltsch of Würzburg in 1867 recorded the frequency with which he found purulent otitis media in infants aged from 16 hours to 1 year. Parrot (1877), in Paris, was surprised how often he found pus in the middle ear of infants at necropsy. In his lectures on "l'athrepsie" he expressed the opinion that there was close association between athrepsia and otitis media: "Soit comme maladie primitive, soit comme complication." Johnston, Brown, and Tisdall (1930) in a clinical study of 171 cases of intestinal intoxication found otitis media in 109 (63.7%), the predominant organism being the streptococcus, which has also been recorded as the chief causative organism in American reviews of the subject. They point out the differences between the symptoms of gastro-enteritis and those of classical primary mastoiditis, and conclude that "intestinal intoxication is not due to masked infection in the middle ears and mastoid antra." Findlay (1932) and Yampolsky (1933) hold the same opinion. Melle (1934) reported on the examination of mastoids in 300 consecutive necropsies in children. In 140 no abnormality was found in middle ears or mastoids, though of this number 62 had died of some alimentary condition. In the remaining 160 pus was found in the middle ear or mastoid. The cause of death in 73 of these had been alimentary intoxication or chronic malnutrition. The remaining 87 of the "pus in mastoid" group had died of causes other than alimentary. In other words, pus in the middle ear or mastoid was not found more often in patients dying of acute alimentary intoxication or chronic malnutrition than in those dying of any other cause. He stated that "from a clinical point of view, and from one's observations at post-mortem, I can see no justification for blaming the mastoid as the primary cause of an acute alimentary intoxication."

Le Mée (1937), discussing Parrot's findings, suggested that the condition was a "post-mortem empyema" and the mechanism one of elementary physics. Cooling of the air in a cavity results in a reduction of pressure, and suction of adjacent fluid (in this case from the pharynx) takes place. Consequently, if looked for, pus may be found not only in the middle-ear cavities but also in the sinuses of infants. Le Mée thought that "the finding of pus in the middle-ear cavities of infants had not the same significance as in the child." Ebbs (1937) examined at necropsy the ears of 880 children aged up to 14 years who had died from a great variety of medical and surgical conditions. Pus was found in the middle ears of just over half of these patients. His series included 603 infants under 1 year, and 61% of them had purulent otitis media when examined after death. A clinical history of "gastro-enteritis" was obtained in 238 infants under 2 years, and 81.4% of these had pus in the mastoids. Further, he found at necropsy that 71.6% of 134 so-called "primary pneumonias" and 70% of secondary pneumonias had otitis media. Ebbs concluded that "otitis media [as found in his series] had played a very large part as the aetiological, complicating, or final cause of death in a great many of these children."

Cooper (1937), investigating infantile diarrhoea clinically in 300 infants, found parenteral infection in 122. Though otitis media was by far the most common infection, "it did not seem to prejudice the outlook." McConkey and Ross Couper (1938) found that of 1,324 infants admitted to hospital, 195 had otitis media or otitis media and mastoiditis, and they thought that the presence of these was responsible for diarrhoea and vomiting in a certain proportion of cases, especially in the toxic groups, caused by "a pent-up infection in the middle ear" and lack of drainage. Campbell and Cunningham (1941), with 574 cases of gastro-enteritis, concluded that "only those parenteral infections found in the early days of illness could be regarded as playing a part in causing the disease."

The question of the association between infantile diarrhoea and vomiting and middle-ear infection has been raised again by Leathart (1943), who believes that "many infants dying from diarrhoea, vomiting, and dehydration have had in addition an unsuspected bilateral mastoiditis two or three weeks before death." He attributes the condition to milk, vomit, or infected mucus entering the Eustachian tube in children either too young or too ill to sit up and accordingly nursed while lying on their

backs. He is convinced that all progressive cases require operative treatment.

The Present Investigation

The patients in this series were mainly infants, and the term "mastoid" is used to include the middle ear and mastoid antrum. Under the age of 2 years there is no sharp division between them, and the mastoid cells are as yet undeveloped.

Except for some patients who died within a few hours of admission to hospital, most survived long enough to allow of full clinical investigation. Careful analysis of the clinical picture revealed no new facts. It is worth noting that 27 of the patients in whose mastoids pus was found post mortem had normal or subnormal temperatures throughout the course of their illness. There was no correlation between leucocyte counts and the presence of mastoid pus as demonstrated after death. Quite low total leucocyte counts were recorded in some cases which had pus in both mastoids. This fact, however, cannot be used as an argument that the mastoid suppuration was "inactive," because total leucocyte counts in infants are often unreliable indices in differential diagnosis.

Many of the "positive" cases had adequate courses of one or other of the sulphonamide drugs, but the clinical course in these patients was unaffected even temporarily. Although sought for in all patients, otitis media was discovered in only 12 patients before death. Pus was found in 71 after death, bilaterally in 38. Of the 120 patients 115 were under 2 years of age.

TABLE I.—*Age Incidence*

Age	Pus in Mastoids	No Pus in Mastoids
4 weeks and under	4	6
5 weeks to 6 months	46	26
7 to 12 months	10	6
1 to 2 years	9	8
3 years and over	2	3
All ages	71	49

As a result of the clinical and pathological diagnoses the cases have been divided into four groups, three of which are fairly well defined, while the fourth contains a variety of conditions.

Group 1: Diarrhoea and Vomiting.—The 49 cases in this group were diagnosed clinically as "gastro-enteritis," and the other pathological findings, mostly inconclusive as regards inflammatory changes, left one with no alternative than to support the clinical diagnosis. Pus was found in the mastoids of 35 of these.

Group 2: Respiratory Conditions (Bronchopneumonia, Bronchiectasis, and Atelectasis).—Of the 30 patients in this group mastoid pus was present in 17, while in 13 the mastoids were clear.

Group 3: Marasmus and Athreptic Conditions.—Six of the 12 cases had pus in the mastoids.

Group 4: Miscellaneous Conditions.—There were at least 20 different causes of death in this group of 39 patients, and here 13 had positive mastoid findings.

Bacteriology

At necropsy each mastoid cavity was swabbed separately and the swabs were examined microscopically and culturally. Attempts have been made by various writers to determine the significance of the bacteriological findings in the pus in cases of latent mastoiditis, particularly so in the symptom-complex of diarrhoea and vomiting of infancy, investigation of the intestinal flora of which so often gives negative results. Floyd (1925), Jeans and Floyd (1926), and Marriott (1925) found haemolytic streptococci to be the predominating organisms in mastoid pus in this condition, and Marriott went so far as to suggest that the infantile diarrhoea and vomiting syndrome was probably a specific intoxication due to haemolytic streptococci, which were found in all his cases. Spahr (1929) concluded that where intestinal organisms were found in cultures of the mastoid pus the prominent symptoms were diarrhoea and vomiting, and that other organisms, though frequently met with, did not give rise to these symptoms. The findings in our series are set out in Table II.

It will be seen that the bacteriology was extremely varied, not uncommonly two or three different organisms being present in one mastoid. There were no characteristic findings in any group, and our results do not support the conclusions of Marriott or of Spahr (loc. cit.). In none of the groups did streptococci predominate, and in the three larger groups pneumococci, either alone or along with other organisms, were most commonly found. Pneumococci were four times as numerous as streptococci in the whole series, and in the diarrhoea and vomiting group were present in 54% of the cases in which there was pus. Crooks and Signy (1936) found the pneumococcus to be the most frequent causative organism in nasal sinusitis in childhood. It is interesting to note that pneumococci were seen in the mastoid pus of one patient with tuberculous meningitis and in one case of meningococcal meningitis. *Bact. aertrycke* was present in one case with diarrhoea and vomiting, but was not isolated from the faeces, and *Bact. coli* was present in three cases in the same group.

TABLE II.—*Bacteriological Findings in Cases with Mastoid Pus*

Organisms Isolated	Group 1. Diarrhoea and Vomiting	Group 2. Respiratory Conditions	Group 3. Marasmus and Athrepsia	Group 4. Miscellaneous Conditions
Pneumococcus	17	3	2	4
" and Bact. coli	2	2	2	
" " Str. haemolyticus.		2		
" " B. proteus				1
" non-haemolytic streptococcus, and H. influenzae				1
Str. haemolyticus	4			
" " and Bact. coli			1	1
" viridans	1			
Non-haemolytic streptococcus	1	1		
Staph. pyogenes		1		
" albus		1		
" pyogenes and Str. viridans			1	
" " " H. influenzae				1
" " " Bact. coli		1		
Bact. coli	3	2		1
Bact. aertrycke	1			
B. proteus	2	1		
M. catarrhalis		1		1
" and Bact. coli	1			
Diphtheroid bacilli	1			
No growth obtained on culture	2	2		3
Total in group	35	17	6	13

Discussion

This investigation was carried out primarily to try to reach some conclusion as to the place "latent mastoiditis" occupies in relation to the diarrhoea-and-vomiting syndrome in infants. Although we have been able to confirm the frequency with which pus is found in the aural cavities at necropsy in these cases, it is almost as common in a wide variety of conditions.

Acute otitis media is one of the commonest diseases of infancy. It is often undetected, sometimes for want of looking, and frequently because the symptoms and otoscopic signs are not as characteristic as in older children and adults. The infant tympanic membrane is tough, and spontaneous perforation is often later in following acute middle-ear suppuration than in older children. Apart from this, however, the anatomy of the infant's aural cavity is such that acute septic processes in it should rarely remain "latent" for long. The otologists teach that, while it is the "chronic ear" in children and adults which develops complications, it is in the acute stage that the infant is most liable to develop local extension of the suppuration. It is generally accepted that acute middle-ear infection in infancy implies involvement of the antrum in most cases. At this age the antrum is quite superficial, and its outer wall may even be deficient where the squamo-mastoid suture lies over it. Subperiosteal abscess should be, and in fact is, a very common complication of mastoiditis in babies. Again, the presence of the unossified petro-squamous suture in the infant presents an easy pathway direct from middle ear to middle cranial fossa. Extradural abscess and meningitis are ever-present dangers, and not rare complications, of acute otitis media in infants.

We think it is an important point that, except for one case of meningitis due to *H. influenzae*, none of our patients had any of the local complications which might reasonably be expected if the pus found in the mastoids was the result of an acute primary active process, and, moreover, so virulent as to cause death from toxaemia and dehydration. Death did

not occur too soon for complications, because the majority survived for over two weeks.

The clinical records in our Groups 2, 3, and 4, where pus was found in the mastoid after death, do not reveal that diarrhoea and vomiting were a feature of the illness, as might be expected if the association of mastoiditis and diarrhoea were that of cause and effect. Indeed, while the "parenteral" infection is well recognized as often being associated with vomiting and diarrhoea in infants, "gastro-enteritis" is not a common associate with, say, a pneumococcal empyema or a staphylococcal osteomyelitis, even when undrained. Why should the same infection in the mastoid cause such profound results?

The shorter, wider, and more patent Eustachian tube is often evoked to explain how milk-infected mucus, etc., can find its way to the middle ear. It seems to us that the reverse holds—namely, that "pent-up" pus is less likely to be present in the middle ear of infants than in older patients, because some drainage can take place through the tube into the pharynx. In fact, this is possibly one of the reasons why classical drum signs are often absent in infants with acute otitis media.

Infants have fairly well developed antral, ethmoid, and sphenoidal sinuses. While clinically recognizable "sinusitis" is not common in infants, it would seem logical to suspect these also as being the seat of "pent-up" infection. Ebbs (1937) has shown that pus can be found in one or more sinuses at necropsy in a by no means negligible number of patients. In the age group he investigated the findings were positive in 30.6% of 496 cases examined. We agree with Findlay (1932) that the climax of the "focal sepsis" theory was surely reached when Odeneal (1928) stated that the nasal accessory sinuses are infected in 50% of cases of gastro-enteritis, and that if myringotomy and mastoidectomy do not cause improvement in the infant's condition the sinuses should be opened and drained!

The diversity of organisms found in our cases and in other investigations makes it difficult to believe that such a constant syndrome as infantile diarrhoea and vomiting can be the result of such infection. Finally, the highly infectious nature and the mode of spread of gastro-enteritis in infants' wards in hospital form, we think, one of the strongest points against latent mastoid infection being the key to the aetiology of this condition.

Summary

In a series of 120 necropsies in infants and young children pus was found in the mastoid cavities of 71.

Though the highest incidence was in patients with a clinical history of "diarrhoea and vomiting," it was found almost as often in a wide variety of conditions.

Clinical, post-mortem, and bacteriological findings suggest that so-called "latent mastoiditis" is not an aetiological factor in the diarrhoea-and-vomiting symptom-complex.

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The Club for Research on Ageing has received from Lord Nuffield a donation of £3,000, which will enable Dr. V. Korenchevsky to continue his gerontological investigations for a period of three years. Clinical trials of the effects of vitamins on aged persons at the Tooting Bec Hospital will be finished at the end of this year. These were rendered possible during the last two years by substantial grants from Lord Nuffield and the Nuffield Foundation. The Club expresses its heartfelt thanks for these benefactions, and is also very much indebted to the London County Council for most valuable co-operation.

SECONDARY ABDOMINAL PREGNANCY

BY

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Secondary abdominal pregnancy is a well-recognized but uncommon complication of pregnancy, and numerous cases have been described in the past. The case here recorded is of interest in view of the complications which had arisen by the time the patient was brought for treatment.

Case Report

On April 22, 1944, a Kanuri woman aged about 30 was brought to the African Hospital, Maiduguri. She complained of twelve months' amenorrhoea, increasing abdominal swelling for the same period of time, and for the last month a purulent discharge from the umbilicus. She did not complain of pain, but on questioning stated that she had suffered from an attack of abdominal pain three months previously, at the approximate time when her pregnancy should have terminated. She did not admit to having had any pain at an earlier period of the pregnancy. On examination the woman was seen to be extremely ill and considerably dehydrated. Her temperature was 99° F. and pulse rate 120 a minute. There was a swelling in the abdomen which appeared to be a pregnant uterus up to the level of 3 in. below the ensiform cartilage. There was a purulent discharge from the umbilicus, from which a portion of a foetal foot was protruding. Traction on this produced the whole foot as far as the ankle-joint. The skin of the foot was somewhat macerated. Over the whole of the left side of the abdomen were well-marked gas crepitations, which extended to well beyond the nipple line. There was a copious and offensive vaginal discharge.

The woman was taken to the theatre immediately, and under light chloroform anaesthesia the small opening in the umbilicus was enlarged upwards and downwards for about 2½ in. each way. This revealed a large cavity full of pus and lined with thick granulation tissue. A macerated foetus was extracted and the cavity washed out with saline, hydrogen peroxide, and finally eusol. There was no umbilical cord attached to the foetus or to any part of the gestation sac, and the foetal umbilicus was closed. The gestation sac was not within the uterus, and there was no opening out of the sac other than that through the umbilicus, which had been enlarged at the operation. The anterior wall of the gestation sac consisted of the anterior abdominal muscles and skin only. The wound was loosely sutured by silkworm-gut stitches through all the layers, and a large drainage-tube was left in the cavity.

The patient was returned to bed and given anti-shock treatment. Rectal saline was administered several times in the first 24 hours and was retained well. To counteract the general infection and the gas infection of the abdominal wall 20 c.cm. of 10% soluseptasine was given immediately and 10 g. of sulphanilamide daily by mouth for the first two days. Antitetanus serum, 3,000 units, was given on admission, but no anti-gas-gangrene serum was available. The sulphanilamide was reduced to 5 g. daily on the third and fourth days and then to 4 g. daily for a further four days. The cavity was washed out at first thrice daily with hydrogen peroxide followed by eusol, and the vagina was douched twice daily with weak potassium permanganate. Recovery was far more satisfactory than could reasonably have been expected. The toxaemia diminished rapidly and the gas crepitations had disappeared within 48 hours. The tube was removed on the fifth day and the stitches on the eighth. By this time the wound was being syringed out once daily and the discharge had decreased considerably. The vaginal discharge had almost ceased. During this week routine examinations of the blood and faeces resulted as follows. Blood: no malaria parasites seen; haemoglobin 40%. Faeces: ova of *Ancylostoma duodenale* and live *Trichomonas intestinalis* were both present in considerable numbers. Treatment of the anaemia was instituted immediately, and at a later date the ancylostome infection was treated successfully with oil of chenopodium.

Convalescence was naturally slow, for the patient had been very debilitated. On May 1 she developed a bed-sore over the sacrum which took six weeks to heal. The abdominal wound healed slowly and a sinus persisted which required to be laid open and packed with bipp. She was discharged from hospital on June 17, by which date the abdominal wound was healed. The haemoglobin was then 65%, and there was no evidence of hookworm infection.

Discussion

Secondary abdominal pregnancy—i.e., continuation of pregnancy within the abdominal cavity following rupture of a tubal pregnancy—is described as being of two varieties—intraperitoneal and intraligamentary, depending on whether the tube

ruptures into the peritoneal cavity or between the layers of the broad ligament. In the intraperitoneal variety the gestation sac is formed mainly by inflammatory tissue laid down on the outside of the amnion. In the intraligamentary variety, as the sac enlarges it displaces the peritoneum upwards and, if lying anteriorly, will strip the peritoneum from the anterior abdominal wall. The pregnancy may continue for a normal period of nine months, after which time a false labour occurs and the foetus dies. After the death of the foetus, if the sac remains sterile, the foetus will become inspissated and in the course of years be converted into a lithopaedion. Infection of the sac is apt to occur at any time from the bowel, uterus, or vagina. In such cases fistulae may form between the sac and one of these other structures. Infection from the bowel is probably more likely to arise in the intraperitoneal variety, for in this type the bowel is adherent to the sac wall.

In the above case the pregnancy was probably of the intraligamentary variety. Furthermore, it is probable that the infection had come from the vagina; for, although no fistulous opening was seen, it is likely that a small opening did exist. It is almost certain that at the time of the false labour some vaginal interference had been attempted by the patient's friends and relations. Any such interference would have taken place under the most septic conditions. The presence of a vaginal fistula would account for the profuse and offensive vaginal discharge, which cleared up at about the same rate as the discharge from the gestation sac.

Summary

A case of secondary abdominal pregnancy, complicated by infection of the sac and rupture through the umbilicus, is described.

A short reference is made to the types of intra-abdominal pregnancy and to the ways in which these may terminate.

The case described is classified as the intraligamentary variety, and the probable source of infection is indicated.

Medical Memoranda

Gas Gangrene after Amputation under Refrigeration Anaesthesia: A Warning

Many surgeons are adopting the freezing method to anaesthetize a limb before amputation. There is no doubt that in certain cases, notably diabetic gangrene, this has distinct advantages. The following case shows that unsuspected danger may lurk even here.

On July 23, 1944, I performed an amputation of the right leg through the middle third for spreading diabetic gangrene of the second and third toes. The patient was a man aged 75, in good general condition. The operation was performed with routine pre- and post-operative refrigeration technique, and first of all went well. Forty-eight hours afterwards, however, he became very ill, and on examination presented the clinical picture of a well-established gas-gangrene infection of the stump. The condition appeared to be beyond surgical scope, and the patient died 12 hours later in spite of the administration of large doses of anti-gas-gangrene serum. Cultures of the muscles during life showed *Cl. welchii* with typical stormy clot formation. In seeking the source of infection we had the ice examined. A bacillus showing the cultural and biochemical features of *Cl. welchii* was isolated. Subsequent examination, on different days, of two further specimens of ice, taken from the centre of a new block immediately on delivery with strict aseptic precautions, gave the same result.

Numerous amputations had previously been done at the hospital, using ice from the same source, with no untoward result. It thus seems that any surgeon proposing to use the method should first make sure the ice supplied is free from pathogenic bacteria—especially spore-bearing varieties. Most of the ordinary pyogenic bacteria probably succumb to the usual skin-cleansing on the theatre table. Ice may be contaminated from its container or during transit from the factory (although better than in Continental cities, there are still a few open ice-carts about, and still a few horses to enrich the dust of London streets); but in this case the contamination has been proved to be *in* the ice. The matter is being taken up by the makers and will shortly be put right, no doubt.

North Middlesex County Hospital. E. KIRZ, M.D.Prague.

Reviews

SURVEY OF BIOCHEMISTRY

Annual Review of Biochemistry. Vol. XIII. Editor, James Murray Luck; Associate Editor, James H. C. Smith. (Pp. 795. 31s. 6d.) California: Stanford University Press; London: H. K. Lewis and Co.

With 90 more pages than the previous volume (reviewed in the *Journal* on July 22, 1944) the new one again presents certain now valued and expected features, along with the pleasant air of novelty imparted by certain of the more specialized chapters. Anglo-American collaboration is, as before, in evidence: three of the chapters are by British experts, one by a Canadian, one by a Puerto Rican scientist, and the others by authors in the United States. The editors have continued their established practice of changing almost all the contributors, even for those subjects that are repeated year by year—a practice that editors of annual reports and reviews elsewhere might bear in mind. Thus D. E. Green and P. K. Stumpf take over biological oxidations and reductions from F. Lipmann; W. Z. Hassid the chemistry of carbohydrates from H. S. Isbell; H. Neurath and J. P. Greenstein the chemistry of proteins and amino acids from L. F. Hewitt, R. A. Kekwick and A. S. McFarlane; E. A. Evans jun. carbohydrate metabolism from H. J. Deuel jun.; R. H. Barnes and E. M. MacKay fat metabolism from G. O. Burr and R. H. Barnes; C. P. Berg the metabolism of proteins and amino acids from H. Borsook and J. W. Dubnoff; J. C. Keresztesy the water-soluble vitamins from R. J. Williams; W. C. Russell the fat-soluble vitamins from K. Hickman; W. H. Sebrell nutrition from C. S. Lanford and H. C. Shermann; F. J. Richards the mineral nutrition of plants from D. I. Arnon. For a reason that close examination of both texts has failed to reveal, the chemistry of the lipins discussed last year by S. J. Thannhauser and G. Schmidt, is this year replaced by the chemistry of the lipids from the pen of J. B. Brown. If the two terms are interchangeable, one is superfluous; if they are to be differentiated, perhaps the editorial board would decide and declare how. This year's article, it should, however, be said, is as interesting as last year's. Again, R. A. McCance and E. M. Widdowson have chosen in the present volume to write on "Mineral Metabolism," whereas in Volume XII L. A. Maynard and J. K. Loosli took the same terms of reference under "Mineral Nutrition." "The Chemistry and Metabolism of the Compounds of Phosphorus" is this year contributed by A. A. Green and S. P. Colowick in place of last year's analogous review of sulphur compounds by J. C. Andrews.

So much for the staple foods: there are as well a number of attractive side-dishes. T. Mann and C. Lutwak-Mann on non-oxidative enzymes; H. S. Loring on nucleic acids, purines and pyrimidines; D. Burk and R. J. Winzler on the biochemistry of malignant tissue; E. L. Tatum on the biochemistry of fungi; D. Glick on histochemistry—all these provide scientific titillation for those palates with a taste for the theoretical or laboratory side of biochemistry, as does the chapter on steroids by F. C. Koch. (Incidentally, it is good to see this term, first proposed by the British scientists R. K. Callow and F. G. Young, now generally adopted.) Others more concerned with the possibilities of therapeutic application will turn with appetite to "The Alkaloids" by R. H. F. Manske; "Synthetic Drugs—Antispasmodics" by F. F. Blicke; "The Chemistry of the Hormones" by H. Jensen; while the more botanically or agriculturally minded will find satisfaction in C. F. Huffman's and C. W. Duncan's chapter on deficiencies of farm animals, in "Chloroplast Pigments" by H. H. Strain, "Growth-regulating Substances in Plants" by J. van Overbeek, and "Photoperiodism in Plants" by K. C. Hamner.

A feature of interest about the authors of this volume is that they are drawn from all types of scientific institutions—Governmental, academic, and industrial. Naturally the academic workers predominate, even when allowance is made for the fact that the staffs at many State colleges in the United States are, strictly speaking, Governmental employees. It is, however, worthy of note that five of the experts (out of

the 34) contributing to the book are on the scientific staffs of manufacturing companies in the chemical or allied industries.

Altogether, as hitherto, this review strikes awe and admiration into the reader's heart: awe at the mass of data necessary to establish even the smallest fundamental advance in science; admiration for the energy and enthusiasm of editors and reviewers who provide a running record of the data, with commentary, a process as essential to the advance as the accumulation of the data themselves. This volume is indispensable, like its predecessors.

AN ADVENTUROUS LIFE

A Man who Found a Country. By Dr. A. Nakashian. (Pp. 279. 12s. 6d. net.) London: George Allen and Unwin, Ltd.

The country which the author of this dramatic tale "found" is the U.S.A. He reached it after a most adventurous life of strenuous endeavour, imprisonment, fleeing from danger, and Armenian massacres. His father was an Armenian carpenter, and at an early age the author came under the Christian influence of American missionaries. They had at that time begun to take a leading part in introducing liberal education in the Near East, especially among the Moslems. Their work among Mohammedans was difficult, death being the penalty for accepting the Christian faith. So the missionaries turned to the Armenians, who were religious by nature and had already an established Orthodox Church. The geographical position of Armenia made it a target for attacks from Persians, Mongols, Romans, Saracens, and Turks. Armenia was the highway between Europe and Asia and the battlefield on which all races had fought for twenty centuries.

Young Nakashian first graduated from an American college and hospital at Aintab, and from there went to the American University at Beyrouth. He became M.D. in 1894, and then had to go to Constantinople to take the State examinations of Turkey before the Imperial Faculty, entailing a further course of five years. His professional career from the time he started medical and surgical practice was one long series of thrills among sheiks, rich merchants, robber chiefs, and Kurdish outlaws. After being imprisoned by the Turks and escaping from the massacres of Armenians, he eventually became a doctor in the Turkish Army in the last war. Finally he left that tottering empire for the United States, where he is now settled as a citizen.

The tale is exciting throughout and bears the imprint of truth, even though much of it is stranger than fiction.

ENDOMETRIOSIS

A Study of Endometriosis, Endosalpingiosis, Endocervicosis, and Peritoneo-Ovarian Sclerosis. A Clinical and Pathologic Study. By James Robert Goodall, M.D., C.M., D.Sc., F.R.C.O.G. (Pp. 140; illustrated. 35s.) London: J. B. Lippincott Company.

Twenty years ago few medical students were taught anything about endometriosis. We now know that this condition is one of the more common causes of pelvic disorders requiring major surgery. Though its clinical manifestations are varied and numerous and its pathology is far from fully understood, none the less it is being diagnosed with progressively greater accuracy. Much of this advance in knowledge is due to the work and writings of Dr. Goodall, whose new book *A Study of Endometriosis* is assured of a warm welcome in all English-speaking clinics. Dr. Goodall gives a comprehensive survey of endometriosis in all its forms, and describes in addition related pathological entities which he terms endosalpingiosis, endocervicosis, and peritoneo-ovarian sclerosis. At this stage of our knowledge it is inevitable that facts and theories should be closely associated, but the author has endeavoured with success to avoid unjustifiable dogma on the one hand and the confusion of facts and opinions on the other. He describes endometriosis, endosalpingiosis, and endocervicosis as invasive diseases of urogenital origin, and subdivides endometriosis into two main groups—mixed and stromatous—either of which may occur within the uterus or, as an extra-uterine manifestation. An acute stromatous endometrioma is also described. This would be diagnosed as a sarcoma by most pathologists, many of whom may not be entirely convinced of the error of their ways even after reading the author's views on the cases he presents. The description of extra-uterine endometriosis is particularly good One small point of criticism is with the statement that in bowel endometriosis as compared with carcinoma of the bowel there is never any unnatural rectal discharge. This is not correct, for an endometriosis of rectum or colon may reveal its presence by periodic rectal bleeding associated with the menses.

In the next edition it is to be hoped that the author will make clearer his views on three important issues. It would appear from his description of endometrial endometriosis that he would include under this heading cases of Schroeder's disease or metropathia. The idea has some appeal, but it would be helpful if Dr. Goodall would state his views on this subject more definitely. His description of endosalpingiosis recalls the work of Frankl, of Vienna, on the subject of nodular salpingitis following recurrent tubal infection, usually of gonococcal origin. No reference is made to this work, and it would be helpful to know if Dr. Goodall is describing the same condition, believing the aetiology to be different from that suggested by Frankl. Finally the reader is left with the impression that all blood cysts of the pelvis are of endometrial origin. King, of Melbourne, many years ago advanced impressive arguments for considering that this was not so. No reference is made to his work, and it would be interesting to know what Dr. Goodall's views are on this subject.

Mention must be made of the excellence of the illustrations, which are so good that it is even a pleasure to turn the book upside down to study Plate IV. This book is sure to stimulate much further research, and the author is to be congratulated on the very high standard of his work.

Notes on Books

MAY and WORTH'S *Diseases of the Eye*, which first appeared as May's *Manual of Diseases of the Eye* in 1900, and of which the present volume is the 9th English edition, is a hardy veteran among the smaller textbooks on ophthalmology. By means of extensive revision the present editor, Mr. M. L. Hine, has succeeded in incorporating the more significant modern work in a text that has obviously proved satisfactory. Inevitably there is a certain unevenness in the style, but the volume remains as acceptable as ever as an elementary guide. It is published at 16s. by Baillière, Tindall and Cox.

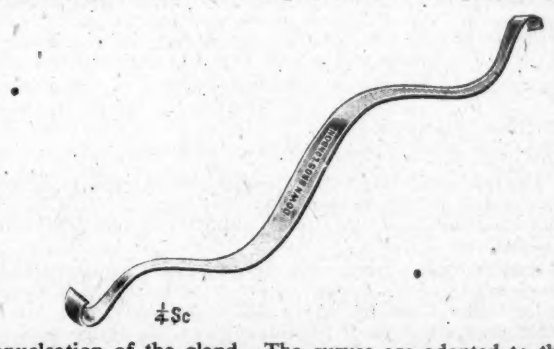
A second edition of *Functional Disorders of the Foot*, by FRANK D. DICKSON and REX L. DIVELEY, has now been published (J. B. Lippincott Company; 30s.). There is very little change from the former issue; one or two new surgical procedures are described—e.g., the Young operation for pes planus, and excision of the digital neuroma in metatarsalgia. There are also two new chapters relating to foot troubles in industry and the Services. The paper is of rather poorer quality than that previously used, probably a wartime measure; in consequence some of the *x*-ray pictures have failed to reproduce as clearly as in the first edition.

Preparations and Appliances

RETRACTOR FOR PROSTATIC POUCH

Mr. CHARLES E. KINDERSLEY, F.R.C.S., surgeon to the Royal United Hospital, Bath, writes:

The retractor illustrated has been made for me by Messrs. Down Bros., its purpose being to retract the trigonal area and prostatic pouch so that the pouch can be inspected after the enucleation of the gland. The curves are adapted to those of the pelvic cavity, and I have found it extremely useful in making the final inspection of the cavity.



MEPACRINE FOR MALARIA

We print below a statement on the present position of mepacrine in the treatment of malaria which has been issued by the Medical Research Council Committee on Malaria.

In view of the great importance of malaria for warfare in the Far East and also in the Mediterranean region, a great deal of work has been carried out during recent years to evaluate the relative merits of the two chief antimalarial drugs available at the present time—namely, mepacrine (atebrin, quinacrine) and quinine. The conclusions reached are shown by the resolutions (reproduced below) which have recently been adopted by the appropriate official bodies in the United States and in this country.

According to the *Journal of the American Medical Association* (1944, **125**, 977) the Board for the Coordination of Malarial Studies adopted the following resolution concerning the relative value to the armed Forces of mepacrine (quinacrine hydrochloride *U.S.P.*), quinine, and totaquine (*U.S.P.*).

"On the basis of controlled quantitative studies in civilian, Army, and Navy establishments, the evidence at hand justifies the following statement:

1. *In the Suppressive Therapy.*—Mepacrine (atabrine) has proved to have all the antimalarial properties ascribed to quinine in the suppression of malaria during and subsequent to exposure to infected mosquitoes. Effective suppression can be accomplished over long periods of time by proper use of mepacrine. Available evidence indicates that this end may be achieved without danger to the individual. Earlier reports indicated a significant incidence of gastro-intestinal disturbances in certain groups of men receiving suppressive mepacrine therapy. For practical purposes these adverse reactions can be avoided by proper administration of the drug. Quinine, in doses adequate to assure suppression of malaria equivalent to that produced by mepacrine in the dosage currently used by the armed Forces, is frequently attended by symptoms of cinchonism. Mepacrine has been demonstrated to prevent consistently the development of falciparum malaria when the drug is administered in proper dosage before, during, and after exposure.

2. *In the Therapy of the Acute Attack.*—Experience in the past two years has demonstrated conclusively that mepacrine (atabrine) when properly administered is fully as effective as quinine in the termination of the acute attack and is safer than quinine. The intramuscular injection of mepacrine is highly effective in securing a rapid therapeutic response. Evidence is not at hand to decide on the relative merits of mepacrine administered intramuscularly as compared with quinine administered intravenously in patients with fulminating cerebral malaria.

3. *In the Therapy of Vivax Malaria.*—Neither mepacrine nor quinine can be relied on to prevent relapses in vivax malaria following the discontinuation of therapy, although the interval between attacks is significantly longer following mepacrine than following quinine in the dosage schedules currently used by the armed Forces.

4. *In the Therapy of Falciparum Malaria.*—There is convincing evidence that mepacrine not only suppresses the clinical symptoms of falciparum malaria but also cures this malignant form. The evidence of a similar curative effect of quinine is not conclusive.

5. *Totaquine* (*U.S.P.*).—Because of its content of crystallizable cinchona alkaloids, totaquine (*U.S.P.*) has activity which approximates that of quinine and therefore can be used as a substitute for quinine when given orally. The antimalarial activity of totaquine (*U.S.P.*) is dependent on the amount of crystallizable alkaloids in the preparation rather than on the specific amount of each individual alkaloid. Gastro-intestinal disturbances occur more frequently following the use of the present totaquine (*U.S.P.*) than they do following the use of quinine or mepacrine.

On the basis of the foregoing statement it is resolved:

1. That no advantage, and possible disadvantage, would accrue to the armed Forces were quinine or totaquine to replace mepacrine for the routine suppression and treatment of malaria.

2. That the large-scale production of quinine or totaquine is not now considered a matter of importance for the management of malaria among Army and Navy personnel. It is possible that a supply of totaquine in excess of the present stockpiles may be required for therapy in civilian populations temporarily under the jurisdiction of the armed Forces in occupied territory where immediate dissemination of information concerning the use of mepacrine (atabrine) is not practicable. In this connexion it should be kept in mind that after the war the overall need for all established antimalarial drugs will continue to be great."

The personnel of the Board is: R. F. Loeb (chairman), W. M. Clark, R. G. Coatney, L. T. Coggeshall, F. R. Dieuaide, A. R. Dochez, E. G. Hakansson, E. K. Marshall jun., O. R. McCoy, F. T. Norris, W. H. Sebrell, J. A. Shannon, and G. A. Carden jun. (secretary).

This resolution was considered by the Drug Prophylaxis and Therapy Subcommittees of the Medical Research Council Committee on Malaria at a joint meeting on Aug. 23, 1944. (The personnel of these subcommittees is: Major-Gen. A. G. Biggam (chairman), Brig. F. A. E. Crew, Col. S. P. James, Dr. W. D. Nicol, Lieut.-Col. B. Maegraith, Col. C. S. Ryles, Mr. P. G. Shute, Brig. J. A. Sinton, Air Marshal Sir H. E. Whittingham, Dr. F. Hawking (secretary). The various items were discussed, and it was agreed that British experience, and the extensive investigations carried out in Australia under the direction of Brig. N. Hamilton Fairley, led to the same conclusions as those which had been reached in America. In particular, the subcommittee endorsed the resolution that if quinine or totaquine replaced mepacrine for the routine suppression and treatment of malaria the change would not be advantageous and might possibly be disadvantageous.

It is not possible during wartime to disclose all the extensive investigations upon which these official American and British resolutions concerning the relative merits of mepacrine and quinine have been based, but when peace returns full details will doubtless be published in the scientific press. Meanwhile the position may be summed up by saying: Under proper administration mepacrine is no more liable to cause serious toxic effects than quinine is; mepacrine is as effective as quinine in the therapy of vivax malaria, but neither compound will prevent relapses at a later date; mepacrine if properly given will practically always suppress and cure falciparum malaria, while the action of quinine in this respect is less certain.

Accordingly it must be realized that mepacrine is not an inferior substitute for quinine forced upon us by the loss of Java, but it is a more effective agent against malaria which would still be employed even if the supplies of quinine were unlimited.

MEDICAL RESEARCH IN SOUTH AFRICA

The annual report for 1943 of the South African Institute for Medical Research, Johannesburg, tells of further expansion of the South African Medical Corps Laboratory Service. This organization now includes seven large and fifteen small laboratories, in addition to the two mobile units based on the institute for field duties. An innovation has been the posting of junior naval medical officers from H.M. hospital ships for short courses at the institute in tropical medical and allied subjects. Among the field units the snake-catchers' section, operating in the Komatipoort area, caught from 50 to 75 cobras and puff adders every month to provide venom for the production of antivenene. The newly formed section of gerbil catchers, working in the Benoni–Middelburg area, caught approximately one thousand gerbils a month for the typhus vaccine department. By the end of the year the monthly production of vaccine was nearly 40,000 doses. Experiments in the prophylaxis of typhoid fever by the intradermal injection of typhoid vaccine proved satisfactory; this method uses less vaccine, and there is neither local nor general reaction.

Vitamin assays revealed that processed cheese is an excellent vehicle for fish-liver oils. The survey of vitamins in African foodstuffs, continued during the year, included the completion of the study of the thiamine content of maize, Kaffir-corn, and other cereals. It was found that the thiamine content of millet is extremely low. Among legumes, the beans to which the native population is especially addicted, notably the speckled sugar-bean and the njugo bean, were found to have the lowest thiamine content.

Mrityunjoy Mitra, ship doctor, has been appointed M.B.E. (Civil Division). The citation in the *London Gazette* reads:

When the ship was sunk by a raider, Dr. Mitra was taken prisoner and after being kept on the prison ship for two and a half months, was interned in prisoners of war camps in France and Germany. While he was on board the prison ship, Dr. Mitra acted as doctor for the 343 prisoners. During his detention in Germany he attended Merchant Navy personnel and in addition had 1,100 other prisoners under his care, mostly Orientals. Dr. Mitra showed exceptional devotion in undertaking this work voluntarily. There is little doubt that he did much to alleviate the sufferings of his fellow prisoners and to maintain general health in the camp, although his own health was so bad that it eventually resulted in his repatriation.

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THE RISE IN PEPTIC ULCER

It is difficult to say anything fresh about the clinical aspects of peptic ulceration. Except for having learned the risks of alkalosis and avitaminosis, we know no more about the aetiology and control than when Sippy introduced his treatment by diet and alkalis in 1915. Since that date, however, peptic ulcer has grown from a clinical problem to a social problem, owing to a secular change in incidence. A rise was already suggested by the large number of cases of haematemesis which came under study in the decade preceding this war. It was hardly possible to doubt the fact of this rise when the present army was recruited and large numbers of men were found to be suffering from peptic ulcer. It was officially stated in May, 1942, that 17% of the total discharges for all diseases from the Army and the Royal Air Force and 13.8% from the Royal Navy were on account of digestive disorders. The majority of these men were suffering from peptic ulcers, and 90% of the ulcers had given rise to symptoms in civil life, before the man joined the Services.[1] In wartime industry men have broken down with peptic ulcer under the strain of long hours or changing shifts, and while the Services can discharge the man with a peptic ulcer the industrial medical officer cannot deal with the situation so simply. No such phenomenon was noted in the last war, either in the armed Forces or in industry, and the only explanation seemed to be a considerable increase in the incidence of peptic ulcer in the years between the two wars. Nor is the increase confined to this country, as is shown by the provision of special dietetic facilities for workers with peptic ulcer in Russian factories and the formation of special units for German troops suffering from digestive disorders.

Nevertheless, in the absence of morbidity statistics, it was still possible for sceptics to doubt the increase in peptic ulceration and compare it with the loose talk about the increase in cancer which had not been substantiated on careful investigation. An analysis of death rates from peptic ulcer in Great Britain was published this year by Tidy,[2] who came to the conclusion that there was little or no rise between 1912 and 1920, but a sharp rise between 1921 and 1930; the curve then flattened out and remained at the same high level. Tidy thought that the rise was almost entirely due to an increased incidence in males over 40. He found certain differences between England and Scotland, more particularly a rather belated increase in the incidence of gastric ulcer in Scotland. When these results were presented at a meeting of the Association of Physicians[3] they were criticized on the ground that certification is liable to be affected by changing fashions and improved diagnostic procedures. This type of criticism has recently been answered by Stocks,[4] who points out that death certification is generally more accurate than certification in life, and that the statistician is interested in long-term trends which are unlikely to be gravely affected by mis-diagnoses and mis-statements. In any event it seems impossible to offer any serious criticism of the factual value of the data on perforation which have been presented by Prof. Illingworth and his colleagues in the article of which the second part appears in our present issue. This is a remarkably thorough piece of investigation which was made possible by the circumstance that the Glasgow region forms a natural catchment area from which practically all cases of perforation flow into a small group of hospitals in the city. It was aided by the high standard of surgical records in these hospitals, which will be the envy of other regions which have tried to compile morbidity statistics. It is clear that perforation of a peptic ulcer was almost unknown in Glasgow until the last decade of the nineteenth century. Since then it has increased in almost exponential fashion to attain a sudden peak in 1940–1, since when the rate has fallen. The main analysis deals with the twenty-year period 1924–43, during which the changes almost entirely concern duodenal ulcer, gastric perforation having remained stationary. The sex ratio has undergone little change, having remained at about 19 males to 1 female throughout. Apart from the rise from a total of 191 perforations in 1924 to 615 perforations in 1941, there are two observations to which we may draw attention. The first is that perforation seems to be related to fatigue, being less common after the summer holiday and the week-end, and more common in the late afternoon; the second is that the fatality rate increases sharply with age.

It is difficult to believe that merely the perforation rate has increased in the Glasgow region, and not the total incidence of peptic ulceration. Nevertheless the papers of Tidy and of Illingworth and his colleagues both point to the need for statistics of the total incidence of peptic ulceration in our population and not just of the fraction which perforates or dies. This implies "filling in forms," which is unpopular with men overworked in practice, but it is the only way in which morbidity statistics can be collected. At present it would be fair to say that we do not know how the incidence of peptic ulceration is affected by climate, occupation, or income level. Such knowledge is desirable in view of the two current theories of causation. These may be defined as the psychological and the nutritional, and both ultimately attribute the blame to our so-called civilization. Donnington has described the characteristic diseases of civilization as psychoneurosis, exophthalmic goitre, hyperpiesia, and peptic ulcer. He attributes their increase to the greater emotional strain of civilized life, and the tendency for feelings to be individual rather than communal, and to be pent up rather than exteriorized. He pictures this pent-up emotion welling up, as it were, in the hypothalamus and expressing itself through the autonomic nervous system and the viscera.

[1] Hurst, A. F., *Medical Diseases of War*, 4th ed., London, 1944.
[2] *British Medical Journal*, 1944, **1**, 677.
[3] *Quart. J. Med.*, 1943, **36**, 260.
[4] *Proc. roy. Soc. Med.*, 1944, **37**, 593.

His theory receives support from Wolf and Wolff,[5] who have made careful observations on a man with a large aperture in the stomach. They found that prolonged emotional disturbances, and in particular internal conflict with unfulfilled desire for aggression and fighting back, were accompanied by marked and prolonged increases in gastric motility, secretion, and vascularity, with reddening and engorgement of the mucosa. It would be generally agreed that nervous tension and fatigue at any rate favour perforation and haemorrhage, and the results of Illingworth and co-workers are in harmony with this view. The importance of diet in the aetiology of peptic ulcer has been unequivocally demonstrated by McCarrison[6] both in the field and in the experimental laboratory. Peptic ulcer is very common in the south of India; it is in fact 58 times as common as in the north. On putting groups of rats on the well-constituted diet used by the Sikhs, and on the defective diets used by the poorer classes in Madrassi and Travancore, McCarrison obtained the following results: first group (Sikh diet), *nil*; second group (Madrassi diet), 11%; third group (Travancore diet), 29% incidence of peptic ulcer. These are remarkable findings, and it is obviously desirable that we should have statistics which would enable us to relate the incidence of peptic ulceration to nutritional status. Many would doubt whether the correlation between peptic ulceration and general poverty of the diet in this country is as close as it appears to be in India. Many would doubt again whether fatigue, nervous tension, and unfulfilled aggression have increased to an extent commensurate with the rise in peptic ulceration.

There are of course other important aspects of peptic ulcer when it is viewed as a social problem. Both water-borne and air-borne infections have been declining as a result of improved social conditions, and developments of chemotherapy have greatly increased our control of bacterial disease. During the last few years virus diseases, like yellow fever and typhus, have yielded to new prophylactic measures, and we can probably look forward with confidence to the eventual conquest of infectious disease. The population is shrinking and ageing, and we are coming to the stage where we are getting rid of acute disease, where our patients live to be older, and where their illnesses by the very fact of age are less tractable and of longer duration. The mortality of both haemorrhage and perforation of a peptic ulcer is directly proportional to the age. Changes in type of disease and in age of population are combining with a real increase of incidence to make peptic ulcer one of the most important diseases in this country. Similar morals could be drawn from a study of rheumatism or mental disease. In planning a medical service and making our hospital provision we must make sure that we are providing for the present war against disease and not the past. There is a tendency in some quarters to speak as if "long-term sickness" could be divorced from general medicine; the lesson from peptic ulcer is that long-term sickness may well be the most important problem of the coming years.

[5] *Human Gastric Functions*, New York, 1943.
[6] *Nutrition and National Health*, London, 1944.

MEPACRINE AND MALARIA

After the great researches of Ehrlich and his successors which led to the discovery of the various arsenical and other compounds used in the treatment of syphilis and sleeping sickness the progress of chemotherapy seemed to halt, and during most of the nineteen-twenties no further notable advance took place. One fresh product—pamaquin (plasmoquin)—appeared which promised new things in the treatment of malaria and was remarkably effective in the laboratory infections of canaries with *Plasmodium relictum*. When applied in human malaria it proved to have only slight curative action and to be very toxic; its discovery, although encouraging, was of little real value to clinical medicine. A much more substantial contribution to medical science was made about 1932, when from the I.G. Farbenindustrie came an account of the antimalarial action of a new substance first called "erion," then "atebrin," and now officially designated as "mepacrine" in the *British Pharmacopoeia* and as "quinacrine" in the *United States Pharmacopoeia*. Mepacrine is composed of an acridine nucleus with a long side-chain ending in a substituted amino group; it is strongly basic and acts in many ways like a yellow dye, tending to stain the skin that colour when it has been taken by mouth in large quantities. According to the original statement of the manufacturers its action against malaria was as powerful as that of quinine, and this was confirmed during the malaria epidemic of Ceylon in 1935, when mepacrine was first tried out on a large scale. From the experience gained in this epidemic and from field trials organized in Malaya and elsewhere, it became generally accepted that mepacrine was about as effective as quinine in the treatment of acute attacks of malaria. It had an advantage over quinine in that it was less apt to cause vomiting and less likely to be followed by blackwater fever; but, on the other hand, its action was rather slower, and in a small proportion of cases it might cause alarming symptoms resembling those of epilepsy or mania. It also had the disadvantage that its prolonged use tended to stain the skin yellow. In the remaining years before the war each compound had its own champions. Some persons and communities relied almost exclusively on quinine and regarded mepacrine with suspicion, but this may have been due mainly to conservatism and tradition. Other groups vaunted the great superiority of mepacrine; but these were mostly German, and their preference often seemed to be based more upon nationalist than upon medical grounds. In parts of the Tropics such as East Africa, where there were large German settlements, a yellow discoloration of the skin began to acquire the significance of a demonstration of patriotism, apparently without any qualms about the resulting non-Nordic appearance. Among more detached observers the general view prevailed that mepacrine and quinine were about equal in their merits and demerits.

With the coming of the second world war and the Japanese onslaught on Occidental possessions in the Far East and the Pacific the problem of the prevention and treatment of malaria became of the utmost importance. The broadcast of the Australian Premier is now well known in which it was stated that 80% of the Australian Forces

first landed in New Guinea were laid low with malaria; and the importance of disease (50% malaria) in causing far more casualties than the enemy had done was similarly disclosed in Mr. Churchill's description of the recent campaign in Burma. But while the dangers of malaria had grown, the supply of antimalarial drugs had diminished. The world's supply of quinine came almost entirely from Java, owing to the workings of a monopoly, which, for reasons the ordinary person could not understand, was never challenged by the development of alternative sources. And with the capture of Java by the Japanese the supply of quinine was reduced at one stroke to almost negligible amounts. In these circumstances the Allied nations turned, somewhat unwillingly, to mepacrine, and immense efforts were made on the one hand to expand its manufacture and on the other to explore its full capabilities and limitations. The whole story of this aspect of military medicine cannot be told until hostilities have ceased, but some of the important conclusions reached are shown in the resolutions which have been adopted by the American and British official bodies for the promotion of research on malaria and its treatment; these are recorded elsewhere in this issue. Both bodies have come to the same conclusion, that mepacrine, far from being an inferior substitute for quinine, is in some ways more effective. So far as vivax malaria is concerned the two compounds are about equal in either preventing or treating acute attacks; but neither compound can stop the appearance of relapses after administration of the drug has been discontinued. When employed against falciparum malaria, however, mepacrine, if properly used, will completely suppress or cure the infection; the action of quinine in this respect is less certain. With correct administration the toxic effects of mepacrine are not so much greater than those of quinine as to hinder its use. Both American and British bodies therefore declare that, even if quinine were available, its distribution to the armed Forces instead of mepacrine would not be advantageous and might possibly be disadvantageous. Apparently one of the debts we shall owe to dire military necessity will be this realization of the superiority of the synthetic antimalarial over the naturally occurring alkaloid.

The gratification felt at the satisfactory way in which we have met the catastrophic loss of quinine from Java is somewhat marred by the humiliating thought that the solution of the problem lay in taking advantage of German enterprise and persistence. Although the work of Ehrlich showed the great possibilities of chemotherapy, this new branch of science long continued to lack effective support in this country. The war has given the British pharmaceutical industry a big opportunity to embark upon long-term projects of research and development. There is no shortage in this country of brilliant workers with a high capacity for original thought, and the material resources are not lacking to give them the support and security they need to bring their thought to fruition. What we want to see is the harnessing of all the energies, mental and material, that will help this country to keep the lead in chemotherapy that penicillin had given it. If we criticize the pharmaceutical industry for its lack of imagination in the past we must also criticize the State for its cheese-paring attitude towards the State-supported Medical Research Council, which receives from the Treasury an annual grant of £220,000. Unfortunately in a commercial community the State finds it more tempting to subsidize business than to subsidize brains, in the foolish belief that the prosperity of a country depends more upon the former than the latter. If this suicidal policy is continued in the post-war world then we shall find ourselves outstripped by those countries which have a larger vision.

SULPHONAMIDES AND AGRANULOCYTOSIS

Agranulocytosis is among the rarer complications of sulphonamide therapy, but the risk of such a serious sequel has prompted the general advice to check the white cell count at regular intervals in any patient on sulphonamides for more than one week. It is commonly held that the danger of agranulocytosis is proportional to the total dosage of drug given, but the complication has occurred after total dosage of 18 g. and an average daily dose of 2.3 g. in a collected series of 20 cases.[1] On the other hand, many patients have been given amounts up to 100 g. or more without any untoward effect. More important than large dosage is the duration of treatment. Agranulocytosis has rarely been reported in patients who have had less than nine days' treatment, and this observation, together with the relatively small dosage that may induce the phenomenon, suggests that agranulocytosis is an allergic rather than a toxic manifestation of sulphonamide therapy. It would thus take its place among other allergic reactions to the sulphonamides—e.g., drug rash, drug fever, and perhaps renal complications. The best treatment for agranulocytosis is still a matter for controversy, and it is often difficult to say if any particular treatment—fresh-blood transfusions, pentnucleotide, liver extract—has contributed to the patient's recovery. Sternal puncture may be a useful prognostic guide; if many immature granulocytes are found in the bone marrow when none is present in the peripheral blood the chances of spontaneous recovery are good.

A new attack on the problem is suggested by the experience of Nixon, Eckert, and Holmes.[2] Believing that a patient with agranulocytosis may succumb to secondary bacterial infection because of the absence of phagocytes, they recommenced sulphonamide therapy in three patients —one with scarlet fever and two with primary atypical pneumonia—who had developed agranulocytosis after a primary course of sulphadiazine lasting for two weeks or more. Granulocytes disappeared from the peripheral blood between the 15th and 20th days after treatment was begun, and was accompanied by secondary fever and the typical ulcerative throat lesions. After an interval of a few days sulphadiazine was started again in amounts sufficient to give blood levels of 5–10 mg. per 100 c.cm. (In one case it was at first given intravenously, and the blood concentration of the drug rose to 20–25 mg. per 100 c.cm.) Within 5 to 10 days granulocytes began to reappear in the blood, pyrexia disappeared, and all three patients made good recoveries. Although other ancillary treatments were used, the authors believe that the second course of sulphadiazine was responsible for the ultimate cure by preventing an overwhelming secondary infection. While this may be true, it is also possible that the second course helped to desensitize the patient to the sulphonamide, for it is now becoming accepted that continuance with sulphonamides may desensitize the patient to specific allergic reactions such as drug rash and drug fever. Another point not appre-

[1] Park, R. G., *Lancet*, 1944, 1, 401.
[2] Nixon, N., Eckert, J. F., and Holmes, K. B., *Amer. J. med. Sci.*, 1943, **206**, 713.

ciated enough is that granulocytopenia resulting from severe bacterial infection is not in itself a contraindication to sulphonamide therapy. Treatment in such cases is often followed by a marked rise in the granulocytes as the infection is brought under control.

HEALTH SERVICES IN NORTHERN IRELAND

The Northern Ireland Minister of Health and Local Government has appointed the following to be a Health Advisory Committee for Northern Ireland: Mr. William Allen, Mr. Leslie Arndell, M.Sc., Mr. William J. Bailie, Miss M. A. Beaton, Dr. B. R. Clarke, Alderman Thomas L. Cole, Lieut.-Col. John M. Foreman, L.D.S., Lieut.-Col. A. R. G. Gordon, M.P., Councillor James Hamilton, Dr. J. Stuart Hawnt, Dr. J. M. Hunter, Dr. George G. Lyttle, Miss Dorothy Melville, Dr. F. P. Montgomery, Councillor Patrick Murphy, Dr. J. H. McBurney, Mr. H. I. McClure, F.R.C.S., F.R.C.O.G., Mr. Howard Stevenson, F.R.C.S., M.P., Prof. W. J. Wilson, M.D., Mr. C. J. A. Woodside, F.R.C.S. The Council, of which Mr. Howard Stevenson has been appointed chairman, is to advise the Minister of Health upon the general administration of the health and medical services. Mr. John A. Oliver, of the Ministry of Health and Local Government, will act as secretary. The members of the Council have been appointed in their personal capacity to advise the Minister on the strength of their knowledge and experience. Mr. Howard Stevenson is one of the representatives of Queen's University of Belfast in the Ulster House of Commons. He was chairman of the Select Committee on Health Services which reported this year.

FOOD YEAST

Food yeast, which has recently attracted the attention of the biochemist and nutritionist, has now interested the Colonial Office, who have formed a company, Colonial Food Yeast, Ltd., to grow it on a commercial scale in Jamaica. The object of growing the food yeast is threefold: to provide a cheap source of protein and vitamins for the native populations in the Colonies, to find new uses for sugar and molasses, and to help the sugar industry in Jamaica. The low level of nutrition in the natives of many of our Colonies has long been a scandal, and it is good news to hear that the conscience of the Colonial Office has at last been quickened. The nutritional, research, and commercial aspects of food yeast are set out in a booklet.[1] Food yeast is the dried yeast *Torulopsis utilis*, which for nutritional purposes is preferred to ordinary bakers' or brewers' yeast (*Saccharomyces cerevisiae*) owing to the ease and economy of manufacture and its superior flavour and palatability. It contains a considerable quantity of high-class protein and vitamins of the B complex, of which it is one of the richest sources: 100 grammes or 3½ oz. provide 43 grammes of protein, 2 mg. of vitamin B_1, 5 mg. of riboflavin, and 40 to 45 mg. of nicotinic acid—more than the daily optimum intake of these three vitamins. Its vitamin B_1 content is much less than that of brewers' yeast, which contains 16 mg. per 100 grammes. This is balanced by its high riboflavin content. Food yeast contains the essential amino acids in kind and proportions similar to those found in a good mixed diet. It contains in particular a large amount of lysine, which is deficient in a diet made up chiefly of cereals. Being much cheaper than animal protein—the cost ex factory is hoped to be 6d. a lb.—it offers an excellent means of improving the dietary of populations existing on impoverished diets. Actually the idea of fortifying food with yeast is not new. The Germans used it in 1914–18 as a source of protein for human consumption, and it is believed that they have been making thousands of tons of it annually in this war.

The source of the carbohydrate for the nutrition of the yeast will be molasses, sugar juice, or raw cane sugar from Jamaica, where the factory for the production of the yeast will be erected. It is hoped that it will thus provide an outlet for the by-products of the Jamaican sugar industry: an output of 12 tons of dried yeast a day is aimed at. Food trials on the nutritive value of food yeast have been made. The proteins appear to be as good biologically as those in milk. In one test a group of school-children receiving a third of an ounce of food yeast a day with school milk showed a greater increase in weight than those of a control group receiving milk but no yeast. Food yeast has distinct possibilities in the field of nutrition at home as well as in the Colonies. Its introduction into soups, stews, gravies, etc., not only would improve their flavour but would considerably enhance their nutritive value. It can also be introduced into bread and would afford a better and cheaper method of "fortifying" white bread than the addition of synthetic vitamins. If food yeast is a success in Jamaica we may hear more of it at home.

[1] *Food Yeast: A Venture in Practical Nutrition.* Published by Colonial Food Yeast Ltd. (2s. 6d.)

THE HEALTH OF MANCHESTER

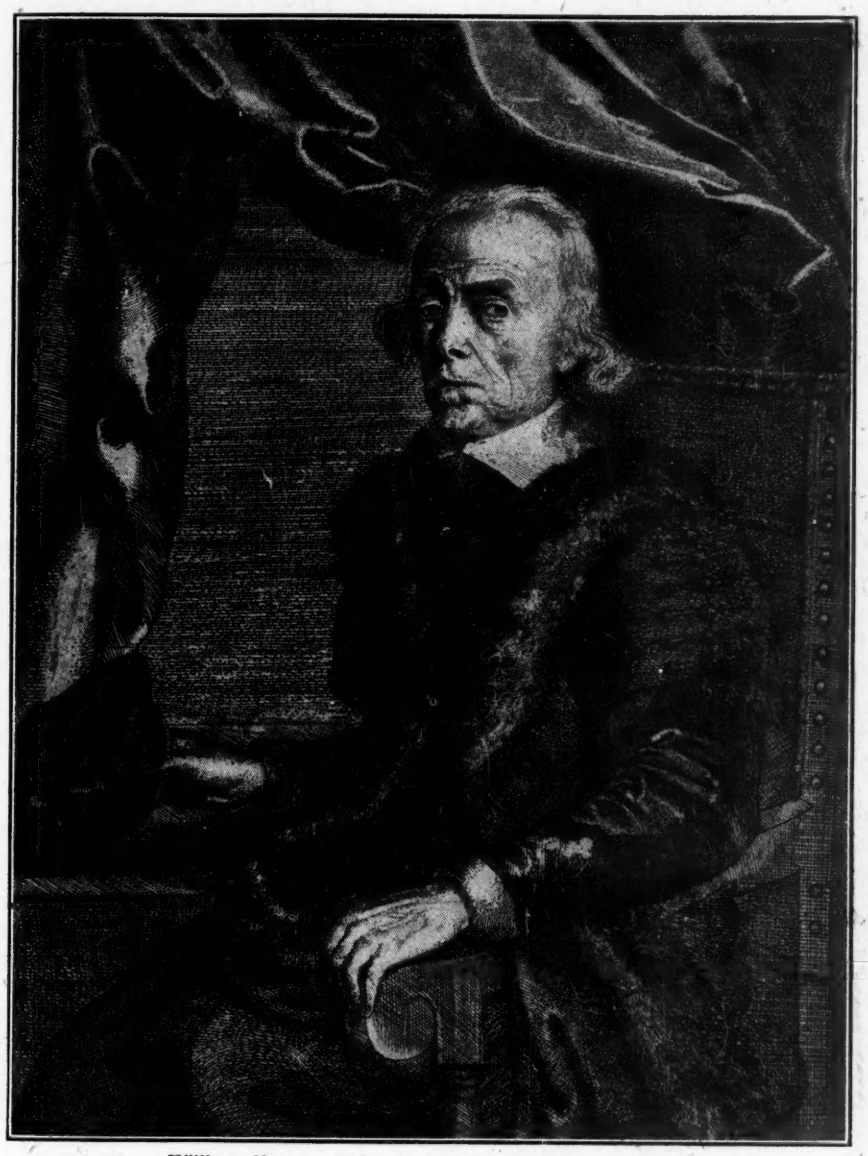
A feature of the report on the health of the city of Manchester for 1943 by the M.O.H., Dr. C. Metcalfe Brown, is a table of the vital statistics for Manchester since 1911. During these thirty-two years the birth rate has declined from 26 per thousand of population to 18.66, which itself is higher than for any year since 1926; the infant death rate has fallen from 156 per thousand births to 61, which is the lowest figure on record. There have been conspicuous falls in the death rate from all forms of tuberculosis (indeed, the rate has been halved since 1911), typhoid and paratyphoid fevers, scarlet fever, and all the common infectious diseases, while the death rate from bronchitis and influenza has gone up; that for cancer has doubled, and that for heart disease almost trebled. In tuberculosis the first years of the present war showed a progressive increase to 1.32 deaths per thousand of population in 1941, but the trend has been reversed in more recent years, and in 1943 was 1.07. There was a marked rise in tuberculosis also during the last war. The effect of the great influenza outbreak in 1918 is brought out in this table. The death rate for influenza, which had been about 0.16 per thousand population, rose in 1918 to 3.07, and returned to normal figures two years later.

The report also contains a statement on health centres and this has been approved in principle by the city council. The city architect and the M.O.H. have planned a typical main health centre. The term must not be taken as meaning the kind of health centre which has figured in recent discussions as a centre for group practice; what is meant here is a centre where the various public health clinics, the maternity and school medical services, the health visiting, and so forth can be administered, though it is felt that if the group-practice centres are eventually set up they should be linked with these public health centres so as to ensure efficiency with economy. Manchester is regarded as conveniently divisible into fifteen units, each containing roughly 50,000 persons, and each having one main health centre and four subsidiary ones. The main health centres are first to be constructed, and the construction of the subsidiary health centres will depend upon the policy ultimately to be adopted for a comprehensive health service. From the drawings which accompany the report the centres appear to be spacious and conveniently planned.

Nova et Vetera

THE PORTRAITS OF WILLIAM HARVEY

In 1913 the Oxford University Press published for the Historical Section of the Royal Society of Medicine a study of the *Portraits of Dr. William Harvey*. The preface and the notes which accompanied the reproductions of the portraits were written by the late Sir D'Arcy Power, who believed his compilation proved "that the undoubted and contemporary portraits of Harvey are more numerous than was expected." It seems that Sir D'Arcy Power must have approached his task in a somewhat uncritical spirit, for against his statement may be set the opinion expressed to me in 1937 by the present Director of the National Portrait Gallery, Mr. H. M. Hake, that there was only one well-authenticated portrait of Harvey in existence. Long experience of the problems of portraiture could not fail to engender an attitude of scepticism, but Mr. Hake's view may be unduly cautious. Nevertheless, it establishes a firm jumping-off point for the study of the numerous other claimants to the honour of representing the features of the great Dr. Harvey.



William Harvey, from the etching attributed to Hollar

The portrait in question is the three-quarter-length seated figure, kept, until 1939, in the Large Library at the Royal College of Physicians. This is stated to have been one of three pictures saved from the old premises of the College at the Great Fire of 1666, and if this be true it has an incontestable pedigree. Starting with the premiss that this portrait is the best-authenticated picture of Harvey's features to which all other supposed representations must be referred, it is easy to eliminate some of the pictures included in the compilation of 1913, which reproduces sixteen paintings, one engraving, and the bust in Hemstead Church. Of the paintings, two are obvious recent forgeries—namely, that hung in the Secretary's Room at the College of Physicians, and the one possessed in 1913 by Sir D'Arcy Power himself. I believe it is true to say that this fact was afterwards recognized by Sir D'Arcy. Of the remaining fourteen, five are clearly portraits of other persons at present unknown—namely, those in 1913 at University College, London, at Rolls Park, at Caius College, Cambridge, at the Erich Galleries, and in the possession of Mr. J. P. Cobbold of Ipswich (a copy of this is at Caius College, Cambridge). This process of elimination leaves nine of Sir D'Arcy Power's list to be seriously considered. One of these, now hanging in the Bodleian Library, Oxford, is clearly derived from the R.C.P. portrait, though it was probably made long after Harvey's death. Three others—namely, those at Merton College, Oxford, in the dining room of the Royal College of Physicians, and at the Aberdeen Medico-Chirurgical Society—appear to belong to a different series of portraits which can now be partly elucidated. In 1936 Dr. Walter Radcliffe, of Wivenhoe, Essex, drew my attention to a portrait apparently representing Harvey which had been in the collection of Dr. Mead in the eighteenth century and now belonged to Sir Arthur Wilmot, Bart., of Alresford Grange. The owner allowed the picture to be deposited at St. Bartholomew's Hospital for investigation, and it is still in the keeping of the Treasurer and Almoners. I soon afterwards learned that there was a related portrait in the Hunterian Collection at Glasgow. This picture, also unknown to Sir D'Arcy Power, represents a doctor with a striking resemblance to Harvey seated in a chair in more or less the same attitude as in the R.C.P. portrait. His right hand, however, rests on an open book, one page of which has drawings of two skulls, and beyond him is a landscape containing many buildings, the two most conspicuous of which can be identified as probably the dome of the old College of Physicians and Trajan's Column. Whether the Alresford Grange portrait was copied from this or vice versa it is difficult to determine, but comparison of both with the R.C.P. picture shows among various differences one which could scarcely have occurred if either of them were copied from it or taken from the life. In the R.C.P. portrait the forehead is high and rather narrow. In the Glasgow and Alresford Grange pictures it is wide and rather low. The associated book, or MS., with the skulls, and Trajan's Column seem to have no particular relevance to Harvey, and in Mr. Hake's opinion both pictures represent another, unknown, individual. If this supposition is correct, it eliminates the three last-mentioned pictures of Sir D'Arcy Power's list, as they are evidently derived from the same source.

Only four pictures remain for consideration. One of these is the very pleasing three-quarter-length standing figure in the

possession of the descendants of Dr. Richard Bright at Ditchingham, Norfolk. The face has some resemblance to that of the R.C.P. portrait, but it is not entirely convincing, and Mr. Hake is unable to accept it as undoubtedly representing Harvey. The fact that at one corner are the Harvey arms and William Harvey's *stemma* carries no weight as evidence, since these could have been added at a later date. I am inclined to think that this adverse opinion may be a little too cautious, and would like to accept this picture as a second authentic portrait of Harvey.

Two more of the list—namely, those at the Royal Society of London and at King's Weston, near Bristol—together with a third, unknown to Sir D'Arcy Power and now in the possession of Lord Cottesloe, are partly elucidated by another picture unknown to Sir D'Arcy Power, which has been at the Kent and Canterbury Hospital since 1807. This represents a subject closely resembling the Harvey of the R.C.P. portrait, but more haggard and worried in aspect. The style of the painting is stated to be much later than 1650, so that it is unlikely to have been painted from Harvey during his life. More probably it is a later interpretation of the R.C.P. portrait with variations according to the taste of the copyist, and clearly it is the source of the three other paintings mentioned above.

The sole remaining problem is the picture at the National Portrait Gallery, which was also rejected by Mr. Hake when making his survey. The picture is so badly painted that it would be no great loss to have it eliminated altogether. Recently, however (*Brit. J. Surg.*, 1943, **31**, 39), I have drawn attention to the fact that a little-known etching of Harvey, certainly made in the seventeenth century, and attributed, perhaps erroneously, to Hollar, can be accepted at sight as almost, if not quite, the most vivid and life-like representation of Harvey that we possess. Furthermore, the National Portrait Gallery picture is recognizable as derived from the same source, and both have a good deal in common with the Canterbury portrait. I have tentatively suggested that the National Portrait Gallery picture may be the original of the etching spoilt by later, incompetent overpainting. This theory may perhaps be one day put to the test by scientific methods.

The well-known and somewhat idealized engraving by Faithorne, used as a frontispiece in some copies of the first English edition of *De Generatione Animalium*, 1653, seems to have been taken from the R.C.P. portrait. Harvey and Faithorne were acquainted, and the likeness is probably a good one, so that the engraving may provide important evidence for the authenticity of the painting.

The bust in Hemstead Church may have been made from a death-mask, but it is difficult to get from it much idea of Harvey's appearance during life.

To summarize, therefore, it can be stated:

1. That there is one well-authenticated portrait at the Royal College of Physicians, from which are derived Faithorne's contemporary engraving and the later Bodleian copy.
2. That there are the pictures of a somewhat different personality originating in the Canterbury portrait, which may in its turn have been derived from the R.C.P. portrait.
3. That there is the lost or spoiled original of the admirable etching attributed to Hollar.
4. That, lastly, there is the Ditchingham portrait, concerning which opinion is divided.

All other reputed portraits of Harvey so far known have had to be rejected.

GEOFFREY KEYNES.

Ninety years ago—in October, 1854—Florence Nightingale sailed for Scutari, and on Nov. 4, 1944, U.S. Army nursing and medical officers, accompanied by British colleagues, made a pilgrimage to her grave at East Wellow, near Romsey, Hants, to pay their tribute to the pioneer of military nursing. The United States have some special links with Florence Nightingale: her advice was asked and given during the American Civil War, and she inspired Longfellow's poem "Santa Filomena." U.S. Army authorities, in co-operation with the British Council, arranged for representatives of the nursing and medical staffs of U.S. hospitals in a wide area of Southern England to attend the ceremony. After short addresses at the graveside and the laying of a wreath, the gathering visited Embley Park, Miss Nightingale's home, and saw mementoes of her career, and then took tea with the Mayor at Romsey Town Hall.

INDUSTRIAL MEDICINE AND HEALTH

NUFFIELD FOUNDATION GRANTS TO UNIVERSITIES

One of the primary objects of the Nuffield Foundation is the advancement of health, particularly by the furtherance of teaching and research. In pursuance of this aim the Trustees have offered the Universities of Durham, Glasgow, and Manchester grants totalling £150,000 to assist them to carry out schemes which they have submitted for the development, as soon as suitable staffs can be appointed, of teaching and research in industrial health. These grants will be spread over a period of ten years. Manchester, where it is proposed to create a Chair of Industrial Health, will receive £70,000. Durham has been offered £40,000 for the establishment of a department under a University Reader. A similar amount is being allocated to Glasgow for a subdepartment of Industrial Health within the existing department of Social Medicine. The Minister of Labour and National Service (Mr. Ernest Bevin) has assured Sir William Goodenough (chairman of the Trustees) of his warm approval of the proposal, which he regards as an important contribution to further progress in industrial health.

The maintenance of a healthy industrial population involves the provision of greater facilities for education and research in problems of industrial health. Great Britain has no university department devoted to educational work in industrial health and no facilities for postgraduate training in industrial medicine. In January, 1943, the Select Committee of the House of Commons on National Expenditure on the Health and Welfare of Women Workers drew attention to this lack, stating: "Doctors who are new to industrial work have to learn slowly and painfully by experience many lessons that should and could be taught in courses of preliminary training if such were available." The three university departments which are to be formed should go a long way towards remedying this state of affairs by the direct promotion of teaching and research in industrial health, and should also prove of indirect assistance to the work of the Medical Research Council by creating further opportunities for the carrying out of medical research into specific problems connected with industrial medicine and health.

For the new departments to achieve their objective they will have to maintain close links within their universities with the science and engineering departments as well as with the organization for the teaching of social medicine, because the problems of industrial health are not limited to the field of medicine but relate also to engineering, chemical, and other sciences, and require for their solution the co-operation of both medical and non-medical people in various ways. The staffs of the departments will also have to work in the closest co-operation with such bodies and persons outside the universities as the Factory Department of the Ministry of Labour, the Industrial Health Research Board, local industries, employers, and trade union officials.

EMPIRE CANCER CAMPAIGN

At a recent meeting the British Empire Cancer Campaign allocated a sum of £39,000 for the continuation of cancer research during the year 1945. This sum compares with grants totalling nearly £36,000 for the present year.

The principal grants are as follows: £10,613 to the Royal Cancer Hospital (Free), including the Chester Beatty Research Institute; £8,000 to the Middlesex Hospital; £3,500 to St. Bartholomew's Hospital; £1,800 to the London Hospital; £2,743 to Mount Vernon Hospital and the Radium Institute; £850 to St. Mark's Hospital, City Road; £1,100 to the Marie Curie Hospital; £120 to the Bristol University Cancer Research Committee; £2,300 to the Cambridge University Cancer Research Centre; £1,740 to the Oxford University Cancer Research Centre; £1,125 to Westminster Hospital; and £5,165 for the expenses of cancer research at the Glasgow Royal Cancer Hospital, Glasgow University, Institute of Animal Genetics of the University of Edinburgh, University College, Nottingham, and St. Thomas's Hospital.

The present allocation for 1945 brings the total amount voted by the Campaign at headquarters during the war to approximately £207,000, and this does not include independent expenditure on cancer research by the autonomous branches of the British Empire Cancer Campaign in Birmingham, Yorkshire, Lancashire, Cheshire, North Wales, Northumberland, Cumberland, and Durham.

D. M. Gibson (*Tubercle*, 1944, **25**, 35) records his observations on 283 cases of bone tuberculosis among women and children in Manchuria. The disease showed a predilection for the bones of the hands and feet, the long bones, the spine, and ribs in the order named. Single lesions preponderated, but multiple lesions were frequent. The diffuse spreading type of osteitis was by far the commonest. The great majority of cases occurred in the first three decades of life, with a preponderance in the second and third decades. Conservative treatment was disappointing, but the results of early and radical treatment of the focus were encouraging.

Correspondence

Arsenic in Malaria

SIR,—In his letter in the *Journal* on Oct. 28 Capt. Good raises a question of considerable importance. He mentions his experience of the use of arsenic in cases of induced malaria (*Plasmodium vivax*). A single intravenous injection of neokharsivan (0.45 g.) was invariably effective in terminating the attacks and no relapses occurred. He suggests that arsenical treatment might be tried in cases of malaria, naturally acquired, which do not respond to quinine, etc.

Some evidence of the effects of arsenicals in such cases of malaria was obtained during the last war. A long series of studies in the treatment of malaria was published,[1] commencing in 1917, by a team of workers in this school. The cases we treated were suffering from long-standing infections which had relapsed frequently in spite of much treatment with quinine. In making our tests with any drugs we provided for an observation period of sixty days, with daily examination of the blood, after the end of the treatment; this period was not usually completed because most of the cases meantime relapsed. Among the drugs which we employed was arsenic —for example, novarsenobillon alone, liquor arsenicalis alone, and liquor arsenicalis in combination with strychnine or with quinine.

The novarsenobillon dosage employed intravenously was from 0.45 to 0.9 g. The immediate action of novarsenobillon on *Plasmodium vivax* was strikingly good. In this infection the drug was found to be even more rapid in its effect on the parasites than quinine; a single injection of 0.9 g. caused the disappearance from the cutaneous blood of all stages of the parasites, usually in about twenty-four hours. The ultimate results, however, were most disappointing. Twenty cases of *P. vivax* were given a single injection of 0.45 g.; of these 18 relapsed. Twenty-three cases were given a single injection of 0.6 g.; of these 22 relapsed. Twenty-one cases were given a single injection of 0.9 g.; of these 19 relapsed. It was noted, however, that a combination of novarsenobillon and quinine was more effective than either novarsenobillon or quinine alone. In *P. falciparum* infections novarsenobillon in the same dosage produced no good effects. Fourteen cases of *P. falciparum* malaria were given single injections of from 0.45 to 0.9 g.; the parasites and temperature were practically unaffected. A similar result was obtained in the small number of quartan cases available for treatment. Two patients with *P. malariae* infection were each given 0.9 g. intravenously on two occasions with a week's interval between the doses; there was no evident effect on either the parasites or the temperature.

This evidence, so far as it goes, is against the probability of organic arsenic alone, in the form of neokharsivan, proving curative of natural malaria infections which have relapsed after quinine treatment. On the other hand, the use of inorganic arsenic in the form of liquor arsenicalis combined with treatment by quinine gave a very interesting result, as shown in one of our series. The object of this series of observations was to determine whether or not (the disappearance of parasites from the cutaneous blood and the control of symptoms having been ensured by two initial intramuscular injections of quinine bihydrochloride 15 grains) the daily administration of liquor arsenicalis minims 30 would suffice to prevent relapses (parasitic and febrile). The arsenic was given according to the following plan: two weeks on treatment, one week off, two weeks on, one week off, two weeks on; all cases were able to tolerate this. Continuous administration of 30 minims daily for longer periods than about two weeks had been found to produce signs and symptoms of arsenical poisoning. In all cases parasites disappeared from the cutaneous blood in from one to four days. Of 31 cases which completed the course of treatment and were then observed for sixty days, only three relapsed during this observation period. Adding and counting as a relapse one case which became positive during the treatment period, the total failures were 4 (12.5%). In a control series of 30 cases which were treated by two intramuscular injections of 15 grains of quinine bihydrochloride without the arsenic 70% relapsed.—I am, etc.,

School of Tropical Medicine, Liverpool. D. B. BLACKLOCK.

[1] "Studies in the Treatment of Malaria," Nos. 1–30, *Ann. trop. Med. Parasitol.*, 1917–20, 11–13.

Time of Ovulation

SIR,—I beg to offer the following comments on your annotation on ovulation and fertilization (Oct. 21, p. 537). You state that "ovulation in woman usually occurs about 14±1 days before the onset of the ensuing menstrual period," but you add that "its timing is probably subject to considerable variations." This latter caution should be particularly emphasized, since the generalization that ovulation usually occurs at a specified time before the onset of the next menses has led, and will continue to lead, to serious errors when applied indiscriminately to individual cases. The frequency of variation in ovulation time was clearly revealed in the excellent review of the literature on this subject by Stein and Cohen (*J. Amer. med. Ass.*, 1938, **110,** 257). Owing to this variation, postulation that ovulation *in a given case* occurred 14±1 days before the anticipated onset of the next menstruation is not a reliable method for estimating the age of a young human embryo. For example, Hamilton, Barnes, and Dodds (*J. Obstet. Gynaec. Brit. Emp.*, 1943, **50,** 241), whom you quote, estimated the age of the pre-villous human embryo described by them to be 10 to 11 days largely on the strength of this postulation. I have submitted detailed evidence elsewhere (*Trans. roy. Soc. Edin.*—in the press) for believing that this embryo is probably 12 days old. This age is consistent with the coital history, and would indicate that ovulation in this case occurred earlier than postulated by the authors.

The earliest pre-villous intra-uterine human embryo so far discovered in this country is that described recently by Harding and myself (*J. Obstet. Gynaec. Brit. Emp.*, 1944, **51,** 225), which was estimated from its histological structure and comparison with other human and with macaque monkey embryos to be 9 to 10 days old. This age, taken in conjunction with the precise menstrual and coital history, provides positive evidence that ovulation in this case occurred on the 9th or 10th day of the cycle, and the patient, an intelligent woman, was insistent that her previous periods for as far back as she could remember occurred every 4 weeks ("every fourth Sunday")—a statement which was accepted with the full knowledge of the variability in the duration of the menstrual cycle which may occur even in the same individual. The specimen and history also suggest that in this case ovulation may have been precipitated by the first copulation during the cycle (on the 10th day). If ovulation time had been postulated as suggested by your article, the embryo would have been calculated to be 5 to 7 days old—an age which is absurdly young in view of the developmental stage reached by the various embryonic elements.

The evidence which you bring to bear on this problem since your previous article (*B.M.J.*, 1938, **1,** 344) comprises mainly the discovery of tubal ova, and you state that ten tubal ova have so far been described, and that every one of these has confirmed the accepted view as to the time of ovulation. Presumably the ten ova to which you refer are those quoted by Hamilton and his colleagues (above ref.), including the two described by these authors themselves. I would draw your attention to the fact that five other unfertilized tubal ova have been discovered (Miller, Engel, and Reimann, *Growth*, 1938, **2,** 381; Reimann and Miller, *Arch. Pathol.*, 1939, **27,** 412), to which no reference is made either in your article or by Hamilton. All five of these ova indicated that ovulation occurred 15 to 17 days before the onset of the next menses in these 28-day cycle cases, and, incidentally, it is interesting that one of these ova is claimed by its discoverers (Reimann and Miller) to have exhibited parthenogenetic activities after mechanical stimulation. Further, advice on a "safe period" *in a given case*, based on the generalization that "ovulation usually occurs . . . etc.," is likely to lead to failure in many instances, as is clearly shown in the literature revealed by Stein and Cohen (quoted above).

Finally, you mention a gap in our knowledge of human development in that "no one has yet seen a fertilized human

ovum undergoing early segmentation or during the morula and free blastocyst stages, when it is still in the tube." I would mention, however, that J. Krafka jun. (*Anat. Rec.*, 1942, **82**, 426) described a tubal ovum made up of a solid mass of small cells, 200 to 300 in number, with zona pellucida intact, which he estimated to be 6 to 7 days old.

I hope, Sir, you will bring these facts, which are of both scientific and practical importance, to the attention of your readers so that they may take them into consideration alongside your annotation.—I am, etc.,

Department of Anatomy, University of Sheffield. FRANCIS DAVIES.

Industrial Dermatitis

SIR,—Dr. G. P. B. Whitwell in his letter (Nov. 4, p. 607) writes that it seems to him "strange that some dermatologists, instead of collecting rare and relatively unimportant skin diseases for exhibition at learned society meetings, have not long before [*sic*] taken more interest in workaday medicine and gone into the factories to learn something useful." And more in the same strain. Now, although the Section of Dermatology of the Royal Society of Medicine, of which he is a member, is not specifically named by Dr. Whitwell and his shafts are possibly not aimed at it, yet as it holds more frequent meetings for the exhibition of dermatological cases than probably any other society, it must be considered to come within his "target area." As president of the Section for the time being I should like to point out that we had a discussion on industrial dermatitis on May 21, 1942, opened by Dr. Sibyl Horner and Dr. Silcock, thirteen other speakers taking part. Another discussion on diseases liable to be mistaken for industrial dermatitis took place on June 24, 1943, with Dr. H. MacCormac in the chair. This discussion was introduced by Dr. Sibyl Horner, and the present writer showed 84 photographs illustrating about 30 common skin diseases which are liable to be mistaken for industrial dermatitis. One of the referees for industrial dermatitis subsequently told him that he had seen every one of those diseases certified as industrial dermatitis not once but many times. At this meeting Dr. Swanston described the effect on the skin of T.N.T. and tetryl, etc. During the presidency of Dr. Semon three visits to factories for members of the Section were kindly arranged by Dr. Sibyl Horner and were attended by about the maximum numbers that could be accommodated. These included a screw-and-bolt factory, a shell-filling factory, and Woolwich Arsenal, in June, 1942, July, 1943, and September, 1943, respectively. During my own presidency there has been a visit to Woolwich Arsenal in October, 1943, and cases illustrating various industrial skin hazards have been shown at meetings, and discussions on them have taken place as follows:

1943. Nov. 18, "Occupational Melanoderma" (Dr. G. B. Dowling).
1944. Jan. 20, "Chlorine Acne from Chlorinated Naphthalines" (Dr. J. E. M. Wigley).
Feb. 17, "Cheese Itch and Itchy Cargoes," a paper by Prof. J. A. Nixon discussed by seven members.
May 18, "Occupational Argyria" (Drs. Wigley and Deville).

Dermatologists in this country know that industrial dermatitis forms only a part, though admittedly an important part, of the whole field of dermatology, and it is important that they should keep their perspective and should not neglect the other equally important and much more numerous skin diseases which occur outside the industrial field.

With the very large number of hospital clinics that the reduced numbers of dermatologists remaining in this country have now to deal with, the time available for visits to factories is limited, especially as such expeditions always have to be arranged some weeks in advance.

Dr. Whitwell is a member of the Dermatological Section of the Royal Society of Medicine, so these facts should be known to him, but I think they ought to be set down here in case his letter should mislead others. I hope I have made it clear that at all events some dermatologists do not deserve the criticisms of Dr. Whitwell.—I am, etc.,

A. C. ROXBURGH,
President, Section of Dermatology, R.S.M.

Artificial Insemination

SIR,—Some of your correspondents have recently raised questions concerning the legal position of doctors, donors, or donees who are parties to the procedure of artificial insemination. Not all of these questions permit of direct and definitive answers, in view of the fact that the subject is relatively new to the lawyers and the issues that emerge have not been examined by the courts or discussed exhaustively in the legal press. While recognizing these difficulties, together with the need to provide guidance and assistance to medical practitioners, the council of the Medical Defence Union has devoted much time and thought to exploring the subject, and has considered the advice of its experienced solicitors. A document dealing with artificial insemination in its several aspects has been prepared and is available for members of the Union who communicate with the secretary requesting a copy.

It must be patent to most of your readers, however, that there are serious hazards lying about the path of any practitioner who undertakes to make available to a patient the procedure of artificial insemination. These hazards may be diminished to some extent by the adoption of certain legal precautions directed towards the protection of the professional interests of the practitioner involved, the observance of professional confidence, and the elimination, so far as is practicable, of prospective litigation.—I am, etc.,

ROBERT FORBES,
Secretary, Medical Defence Union.

The Hazard of Anaesthesia

SIR,—I am glad to see that someone with the long experience of Dr. G. Dunderdale in his letter (Oct. 28, p. 578) supports mine of May 6. Both he and I plead for open ether, a good airway, simple armamentarium, and a complete disregard of an impatient surgeon.

I quite agree with his letter, in which he says that only experience can make a good anaesthetist. The present market price of a good resident anaesthetist seems to be about £350 a year: not much attraction for a man of experience! In some hospitals newly qualified men are expected to deal with any emergency; in one I know a man who has never given any anaesthetics has been appointed. In some hospitals the patients are aged and infirm, and if surgical treatment be needed great care is essential when one is dealing with a worn-out heart and chest.

I quite agree with Dr. Dunderdale that tonsil and adenoid operations present great difficulties. In the first place we have to face respiratory obstruction owing to the adenoids, and, secondly, anaesthesia must be induced quickly to avoid nervous shock. After rapid induction, deep anaesthesia must be maintained for a few minutes to enable the surgeon to complete his work.

Whatever agent is used the patient must leave the table with his cough reflexes back, otherwise there is a danger of respiration pneumonia. I get over this problem by using two masks, one soaked in ethyl chloride, the other in ether. The child is under in about two breaths, and deep anaesthesia can be obtained by the ether in a few minutes with the aid of Gamgee tissue over the ether mask. The pupils should be carefully watched, and when two-thirds dilated the child can be left to the surgeon. If one is experienced the child should leave the table coughing. All these and other tricks can be learned only by experience.

Better salaries and full-time experienced anaesthetists is the only answer to this problem.—I am, etc.,

Birkenhead Municipal Hospital, Cheshire. JOHN H. HANNAN.

Drugs and the Doctor

SIR,—The letter from the National Pharmaceutical Union under the above title in your issue of Nov. 4 suggests to the casual reader that when the Pharmacy and Medicines Act, 1941, was in Parliament the Union was fighting a lone battle against the manufacturers of proprietary medicines, who were supported by the Pharmaceutical Society and defended by the Minister of Health. It further suggests that the Society's opposition to control of proprietary medicines was withdrawn

because it wanted to see certain other sections of the Act become law. Had the late Dr. G. C. Anderson been still with us he would have been able to testify to the laborious work of the Society, together with the B.M.A., in a committee under the chairmanship of Sir G. Elliston, in preparing a scheme of control of proprietary medicines. The proposals of that committee went further than the provisions of the 1941 Act controlling those medicines, but the draftsman lifted into the Act many sections from the draft prepared by the committee which met at the Society's house during 1935 and 1936.

In the House of Commons the National Pharmaceutical Union sought at the last moment to secure an amendment which would have confined the sale of new proprietary medicines to chemists. The Society might have desired to support them, but the Bill was an agreed measure between the Government and a number of organizations; and for this reason the Society's hands were tied. The Minister of Health may have "castigated" the Union, but he did so because, rightly or wrongly, he regarded their action as a breach of an agreement. Of the Society he said (*Hansard*, July 16, 1941, col. 688): "When people talk about the National Pharmaceutical Union it might be assumed that they speak for the whole of the chemists. That is not so. There are two bodies, one of them a great professional body, the Pharmaceutical Society, who were a party to all the discussions. There has been no last-minute going back on their agreement on their part. I wish to make that clear."

I am sorry to import the ashes of old controversies into your columns, but the Pharmaceutical Society really cannot allow this imputation upon the part it played in this matter to go unchallenged, and it must invite your readers to compare what the Union now says with what the Minister had to say at the time.—I am, etc.,

The Pharmaceutical Society of Great Britain, London, W.C.1. HUGH N. LINSTEAD, Secretary.

Rate of Artificial Respiration in Cyanosis

SIR,—As Dr. Eve's letter (Oct. 14, p. 510) would appear on casual reading to cast discredit on my article (Sept. 16, p. 366) it is necessary for me to point out that no such views are justifiable, for his letter is not only unclear and ambiguous in vital parts but is also fallacious in its main arguments.

Dr. Eve is unwise to have presumed that I had embarked upon the precarious course of attempting to improve one small aspect of the long-established teaching of artificial respiration without having fully acquainted myself with all aspects of the subject. My whole article *deals only with cases of asphyxia or cyanosis* and not at all with cases without cyanosis, except to exclude them. Thus my statement "that an increased rate can do no harm in any case and must in many cases do much good" refers clearly to cases of cyanosis *only* and not to cases without cyanosis. An increased rate may, of course, produce acapnia in those cases whose respiratory failure is not due to cyanosis, but will not produce it in cyanosed cases (discussed later), hence this irrelevant condition "acapnia" was not mentioned in my article.

Dr. Eve states that my arguments are unanswerable "if one falls into the old error of assuming that the state of a drowned person and his needs are similar to those of a conscious subject. They are quite different." This statement is unclear and ambiguous, and in its present form means nothing *definite* at all. Does Dr. Eve mean a "conscious normal subject" or a "conscious cyanosed subject"? There is a vast difference between the two, and the statement cannot apply to both. If he means a conscious "normal" subject, such as the subjects of his own investigations in 1933, this assumption is indeed an old error still shared by many. I have, however, dissociated myself from this error, for the whole argument of my article is dependent upon the great difference between "cyanosed" and "normal" subjects. If, on the other hand, he means a conscious "cyanosed" subject (as would appear from the context), he has made a grave error. It is quite incorrect to speak of the subjects of my experiments as "normal subjects." These subjects reproduce almost exactly the state and needs which the drowned person has passed through before losing consciousness, and there is *no error* in assuming that the state of a drowned person and his needs are similar to those of a conscious cyanosed subject and that they vary only in degree; the only difference being that in the drowned subject the O_2 is further decreased and the CO_2 correspondingly increased, so that the body cells are further affected thereby, and unconsciousness and respiratory failure have resulted. In both cases respiratory exchanges are required to improve the condition and *only* respiratory exchanges *can* do so—a further proof of similarity. That Dr. Eve still adheres to the old error is shown by the statement later in his letter that "increasing the rate up to 20–22 per minute increased the ventilation but reduced the CO_2 too much." Naturally it would reduce the CO_2 too much in the "normal" subject, but it would not have done so in the "cyanosed" subject to whom the statement is now freely applied.

Writing of the subjects of my experiments Dr. Eve states: "Combustion is active . . . and CO_2 is accumulating in the blood. . . . Respiration has then to be violent to make up for arrears." This increased respiration is necessary because of the cyanosis present. Continuing the quotation: "But in the cold and toneless drownee combustion is in abeyance, the consumption of O_2 is minimal, and very little CO_2 is being formed." Quite true, so far as it goes, but it is here that Dr. Eve makes another serious mistake. He claims that because little CO_2 is now being formed there is little present in the blood, and that increased respiration is no longer required. This is most certainly not the case, and the enormity of such an error is astounding. Has not this cold and toneless subject passed through all the earlier stages of cyanosis leading up to his present condition? What of his "arrears" which required increased respiration (and did not get it) before losing consciousness? Are they not still present, and have they not, in fact been considerably further increased? Therefore is not increased respiration even more required? And if CO_2 is toxic to nerve cells *in extremis* (as stated in Dr. Eve's letter) is this not a further need for increased respiration? Thus Dr. Eve admits that increased respiration is required in the earlier cyanosis but claims that it is not required later in the deeper cyanosis, which is absurd.

Continuing the quotation: "Hence when cyanosis and errors of CO_2 and O_2 have been adjusted by the first few minutes of artificial respiration, overventilation may then easily wash out too much CO_2 and produce a deficiency of it in the blood (acapnia)." This short sentence covers the whole field of physiological changes which take place in the blood and body cells from deep asphyxia until "presumably" acapnia is produced. It is here that Dr. Eve has made yet another grave error, for somewhere in this gradual scale of improving blood conditions (increasing O_2 and decreasing CO_2) is the region in which the subject naturally recovers normal respiratory control and consciousness. Indeed, "when cyanosis and errors of CO_2 and O_2 have been adjusted," be it in few or many minutes, the object of artificial respiration has been achieved, and its performance is discontinued. It is obvious that this stage must be passed through sometime before overventilation could possibly go on to cause acapnia. That there is little danger of the subject being rushed through this stage of fairly normal CO_2–O_2 blood levels into acapnia without regaining respiratory control and consciousness is amply supported by Dr. Eve's statement, *on excellent authority*, that ". . . in some operations apnoea is maintained by hyperpnoea for 20 or 30 minutes without apparent injury from acapnia."

There would appear to be no danger in the cyanosed subject of the increased rate washing out CO_2 in amounts disproportionate to the amount of O_2 that can be absorbed—as does happen in the normal subject—for in the cyanosed subject the O_2 level is very low and the need is very great, so that the blood would take up O_2 as readily as it would part with its CO_2. In my experiments it is seen that eight times the normal respiratory exchanges cause no disproportion between the diminishing CO_2 and increasing O_2; and as no artificial means can provide more than about four times the normal exchanges there would appear to be no danger whatever in such usage for cases of asphyxia or cyanosis. Indeed "Nature's method" cannot be wrong.

Space does not permit me to comment on minor matters raised in Dr. Eve's letter; but I have, I think, clearly nullified his main criticisms. I therefore maintain that there is no practical danger of acapnia supervening as the result of my

suggested increased rate in cyanosis, and that the result of any such rate would be the earlier resuscitation of the subject.—I am, etc.,

Manchester. P. R. TINGLEY.

Atmospheric Conditions and Group Recurrences

SIR,—The interesting note of Dr. G. C. Pether (Nov. 4, p. 608) on three migraine patients having attacks at times of barometric instability opens up a subject dealt with in detail by W. F. Petersen clinically and biochemically (*The Patient and the Weather*, 1934, **2**, 53).

Group recurrences are perhaps best seen in neuralgias, fibrositis, and arthritis in relation to moving cyclonic disturbances (S. Weir Mitchell, *Amer. J. med. Sci.*, 1877, **73**, 305). But study for some years of about 30 cases of leukaemia suggests that some of those frequently recurring do so in groups, simultaneously or nearly so; also there are indications that some cancer patients recur in groups about the same times. This suggests that external cyclic influences (? atmospheric) raise and lower the patient's resistance. This resistance side of cancer has been much neglected, as was suggested lately by Dr. Thomas Lumsden (*Lancet*, 1944, July 15, p. 91), and if there are indeed group recurrences associated with meteorological factors, this might facilitate the attempts to prevent recurrences, in some cases at least (Webster, *Practitioner*, 1942, **148**, 226). The subject is one worthy of further studies.—I am, etc.,

London, W.1. J. H. DOUGLAS WEBSTER.

Mistaken Diagnoses in Infectious Fevers

SIR,—Dr. D. F. Johnstone's article (Oct. 28, p. 555) should be very helpful. May I emphasize, even amplify, a few points from fevers hospital and G.P. experience?

1. *Diphtheria.*—Every acute throat seen early should be swabbed before the conventional and useful mist. ferri perchlor. and pot. chlorate is given. To use the antiseptic first is to burn your boats, both clinical and bacteriological. Swabs should be carried in the bag, and the swabbing should be done after all clinical examination is completed, especially in a child. The time spent is negligible, the gain immense. I have never found bacteriologists complain that I send them too many swabs. A negative swab is not necessarily final: if you are asked to repeat, stop local antiseptics for one day before.

2. *Scarlet Fever.*—The most useful clincher in all cases of doubt is a pulse rapid in proportion to temperature. Remember a fevered pulse does not accelerate much from psychic causes, even in a child. A really fast pulse, whether after childbirth or in a child with a rash, should suggest the streptococcus.

3. *Rubella.*—It is amazing how often a fit of sneezing occurs early in the onset. Small hard glands behind the ear, in a child with a clean scalp, are another clincher.

4. *Measles.*—A sick child should not be fussed about, but an examination of the throat should be made at each visit in this disease to exclude intercurrent diphtheria.

5. *Acute Pneumonia.*—The surgeons could supply the obverse of Dr. Johnstone's medallion. Abdominal pain and rigidity often usher in pneumonia, especially if it is a double. It is a worse mistake to operate than not to operate in cases of doubt, whatever the disease.—I am, etc.,

Edinburgh. A. GUTHRIE BADENOCH.

Débridement

SIR,—If further proof were needed, your correspondence columns show that the meaning of "débridement" is not clear to English surgeons. The term first appears in French surgical literature at the time of Paré and was regularly employed by Baron Larrey in his case reports from the Napoleonic campaigns. It signified incision of the superficial and deep tissues to release tension, and is still so understood by the French. The use of "épluchage" in a surgical sense was introduced during the last war. As you say, it means to clean out, and it is descriptive of what we call "wound excision." The word does not come easily to the English tongue, and perhaps on that account has not been generally accepted here.

In view of these facts I would suggest that in the interests of precise statement and corresponding action it would be well if the use of these foreign terms were abandoned. The procedures in question can be perfectly well described in English, and writer and reader will thereby no longer be left in doubt.—I am, etc.,

Oxford. C. MAX PAGE.

"Skiagram"

SIR,—Mr. McAdam Eccles, in appealing for a universally accepted name for the negative image produced by the action of *x* rays, raises a point which is not without some importance. Those older members of the profession whose youth was, as mine, spent at school, and perhaps also university, entirely in the study of the dead languages, and who retain some reverence for them, will wish to see that the term we use is at least derivatively correct. Mr. Eccles gives a list of 19 names which he says are applied to the product of our labours, and I should have no quarrel with him were it not that in describing what he means by these 19 he adds a twentieth, which is one of the least correct of all—i.e., "a photogram produced by *x* rays." Now, a photogram means "a thing inscribed by the agency of light," and *x*-radiation is as far removed from light as is the radiation of "wireless." What frightens the nervous patient when he enters an *x*-ray room is the belief that a brilliant light is going to flash about him. I would therefore plead for the rigid exclusion of any reference to light which might be implied by the use of such words as "photogram" or the even less correct "photograph."

About half the terms in Mr. Eccles's list can be deleted at once since they end in "graph" as distinct from "gram." The word "graphe" (I do not expect the *Journal* to produce the Greek script) means writing or drawing in the abstract; the word "gramma" means writing in the concrete—i.e., a thing inscribed. Telegraphy means the art of writing from afar; a telegram is a thing written from afar. The word, then, which we choose should end in "gram" and not in "graph"; and here we are at once at a disadvantage. A radiologist should by radiography produce a radiogram, but a radiogram has by a corruption of two wrongly applied words come to mean the commercially produced noise-box of the drawing-room. There it is firmly implanted, and any attempt to rescue it would result inevitably in confusion. I suggest we leave it alone. What then? Roentgenogram? God forbid. It's German; it's grossly ugly; few of us, probably, can pronounce it correctly; and I, at any rate, after 23 years as a radiologist, am never quite sure about its spelling. Surely we need never use so hideous a word because a German once stumbled on a discovery by accidentally fogging a plate? Any Englishman can fog a plate. No, we can do better than that. There remain, then, in Mr. Eccles's list, for practical purposes, only "shadowgram," "actinogram," and "skiagram." The first goes out at once. It is a childish combination of English and Greek—worse than some of the Latin-Greek combinations of medical nomenclature. Actinogram is incorrect because "aktis" means a ray of the sun, which we do not use. There remains, then, only "skiagram," which is etymologically correct: "skia," a shadow, and "gramma," a thing inscribed. And, what is more, the Greeks themselves combined the two words. Skiagrapheo means "I etch out in light and shade." Personally I do not shudder if I am asked for "an *x*-ray," though there are no rays about it and *x* is an unknown quantity. I have got used to it. But if we must have a rather ugly word of classical origin I do not think many radiologists will quarrel with Mr. Eccles and those other distinguished gentlemen who instruct our students if they teach them to ask for a skiagram. But skiagram, please, not the sciagram or skiogram of Mr. Eccles's list. No Greek word ever began "sci-"—and our love is feminine, not masculine.—I am, etc.,

Bedford. H. B. PADWICK.

*** According to Liddell and Scott (6th edition) γράμμα means "that which is drawn"; and γραφή, "properly *a representing by means of lines*." γράμμα, incidentally, also means "a small weight"; hence the French, gramme. The *Shorter Oxford* says of **-graph**: "The bulk of the words in *-graph* are of very recent invention, and have the general sense of 'that which writes, portrays, or records.' . . ." For the "shadow which is recorded" we join with Mr. McAdam Eccles and Dr. Padwick in preferring "skiagram."—ED., *B.M.J.*

Mr. Shaw on Doctors

SIR,—Greatly as I enjoyed reading Prof. Greenwood's criticism of Mr. Bernard Shaw's new book, *Everybody's Political What's What* (Oct. 28, p. 570), I cannot help thinking that both you and the writer of the criticism take Mr. Shaw too seriously. I have read, and greatly enjoyed in parts, all Mr. Shaw's plays, not to mention the lengthy prefaces, and have seen them acted. There is no doubt that the world of drama and literature would be much poorer without them, but to take them seriously would be a poor compliment to this author, who always writes with his tongue in his cheek. In his old age Mr. Shaw has confirmed that his Socialism is no more than a façade, notably in his pathetic letter recently in the *Times*, wherein he complains of the preposterous tax he has to pay on his income of £20,000 a year.

M. Colbourne, in *The Real Bernard Shaw*, a book worth reading, deals at length with the attack of pernicious anaemia which Mr. Shaw contracted and for the cure of which he made no bones about taking liver extract. This is a curious renunciation to have had to make for an antivivisectionist, anti-vaccinationist, and anti everything which science has proved to be of value in the practice of medicine. The words "filth" and "poisons" quoted by Prof. Greenwood mean nothing to Mr. Shaw when necessity compels him to employ such a remedy for his recovery.—I am, etc.,

Norwich. H. J. STARLING.

SIR,—If one may be allowed to criticize, is not Prof. Greenwood's apologia for his profession too ponderous and erudite for most laymen, whereas, in so far as it is designed for his professional brethren, is he not preaching to the already converted? Bernard Shaw has always relied for his effects upon verbal fireworks, paradox, and the denial of the obvious and long-established; and those of us to whom, in our youth, he was a literary idol have, in our middle age, been alienated by those qualities in him which formerly excited our admiration.

The facts of medical science are already, as it were, on the statute book, and need no defence against Bernard Shaw or any other layman.

Does anyone ever take Shaw seriously about anything? Nearly everything he writes has a profoundly irritant effect for the reasons stated above. Need we therefore as doctors be disturbed by his ignorant incursions into medical science?—I am etc.,

Hove. G. L. DAVIES.

Psychology of the "Presser"

SIR,—In the answer in "Any Questions?" (Oct. 21) on the psychology of the man who "presses" at golf your contributor says that this is the result of a longing to do superlatively well, and a parallel is drawn with the "pressers" in everyday life, who are always aiming too high. The remedy suggested is simple persuasion or "more intensive psychotherapy."

On the face of it, this sounds the height of common sense, but I wonder in practice how many "pressers" have ever been influenced to change their ways by such methods. As a supporter of the teaching of Matthias Alexander, I agree with him that in practice the solution is never as easy as is suggested, and that it is not enough to rely on persuasion. Alexander, in his rather bizarre terminology, describes what is here called "pressing" as "end-gaining"—i.e., devoting the entire attention to the end-result to be attained, at the expense of what he calls the "means-whereby." He has devised a delightfully subtle technique for teaching people to turn their attention from the "end" to the "means," and, by reducing activity down to its basic components, he builds up reaction again with the components in the right order.

A satisfactory explanation of "pressing" can be obtained by referring to the hypothesis of the "total pattern of reaction" and the "partial pattern of reaction," as described by the late G. E. Coghill in his *Anatomy and the Problem of Behaviour* (Cambridge, 1929). Briefly, Coghill describes how in the developing amblystoma, the wave of neuromuscular excitation arising in response to peripheral stimulation travels cephalo-caudal from segment to segment, so that in the early stages of neuromuscular maturation the excitation which reaches the limb segments is preceded by excitation in the body segments. The response to a stimulus to a limb, early in the life cycle, will produce a "total reaction" in which the trunk is involved before the limb. However, later on in the life cycle, stimulation of the limb segment will produce a separate "partial pattern of reaction," and the limb moves on its own: during this reaction the "total pattern of reaction" in the trunk is maintained undisturbed, but its maintenance is the essential prerequisite of adequate limb reaction. It is Alexander's contention that a condition of mal-coordination such as is manifested in "pressing" is due to the "partial pattern of reaction" in the limb coming to dominate the underlying basic "total pattern," which should be maintained constant throughout activity: energy which should be devoted to keeping the "total pattern" constant is misdirected into the "partial pattern." In the well-coordinated organism the wave of neuromuscular activity arising from a stimulus is directed first into the total pattern and then on into the partial pattern, and the problem of "pressing" can never arise, because any *increased* effort is directed first into maintaining the "constant" of the total pattern, and only secondarily into the partial pattern by means of which the end is to be attained.

I trust that this explanation does not make Alexander's work sound more obscure than ever, but I myself have found it helpful in explaining his method of restoring a constant element to neuromuscular reaction. It also explains why people *will* persist in a given type of activity long after they have decided that it is valueless, and in spite of their efforts to change. Any increase in effort in these people means that more and more energy is poured into the partial pattern, increasingly at the expense of the total pattern. It is only by teaching such people to cease distorting the total pattern and to work in conformity with it that they can make their efforts to succeed effectual, and can effectively translate good advice into practice.—I am, etc.,

London, N.W.1. WILFRED BARLOW.

Association of Municipal Specialists

SIR,—At a meeting held at the Royal College of Physicians on Oct. 26, 1944, it was decided to form an Association of Municipal Specialists, and that the qualification for membership should be: "Registered medical practitioners who are specialists principally engaged in clinical work, pathology, or radiology, and who are employed whole time by a local authority." It was also decided that the term "specialists" should be defined as those medical men who are looked upon by their professional colleagues as specialists.

I am anxious to get into touch with those who are qualified to become members, and I should be much obliged if medical officers of health would send me, or ask one of their specialists to send me, a list of such persons employed by their local authority. We have no other means of getting in touch with them.—I am, etc.,

12, Manchester Square, London, W.1. GEORGE F. STEBBING, Hon. Secretary.

Registration of Specialists

SIR,—The proposals for the registration of specialists which have been accepted by the General Medical Council (Aug. 5, p. 188) have a direct bearing on the future development of the salaried and private medical services of the tropical Empire, and through them on its whole development.

If a register of specialists is prepared solely as a part of the internal administrative machinery of a National Health Service applicable to the United Kingdom alone, it is right and proper that it should be limited to persons domiciled in the United Kingdom, or normally so but temporarily absent on war service. A statutory entry in the *Medical Register* has, however, a significance much wider than this, as the *Register* is used in courts of law and medical services for the assessment of the qualifications and status of medical people in many parts of the Empire other than Great Britain. The absence of an entry showing classification as a specialist against a practitioner's name will ultimately inevitably be taken to imply his lack of qualification to practise or be recognized as a specialist. I therefore notice with concern that the sole provision for the registration of specialists living abroad refers to those people temporarily absent on war service.

Medical specialties are practised and the necessary experience can be gained in many parts of the Empire. If the Far East is to return soon after the war to its previous state of development, and if the entire tropical world is to rise to a properly developed condition, it is imperative that the hygiene and

medical services should be of the highest standard, because the biggest impediment is still disease. Statutory registration of specialists in the United Kingdom and failure to register those abroad will have serious detrimental effects on these services. It will discourage young men from going to parts of the Empire where they could not secure the recognition of their abilities that they could at home; those living abroad will have a reduced incentive to advance themselves because the unregistered specialist cannot hope for the financial reward in any salaried service that would go to a registered one; as a result, people who have in fact qualified themselves abroad may be expected to return to Great Britain to secure recognition and all the material advantages it will imply. Lastly, it is of interest that it is doubtful whether, on their return to England, either Dr. Patrick Manson or Major Ronald Ross, as they were then, or many other distinguished medical men subsequently returning from the Tropics, would have been entitled to practise as specialists.

It may be answered that the position will adjust itself by newly qualified practitioners staying in Great Britain until they have secured specialist status, and then proceeding abroad. Though this would occur to some extent, as a full solution it would be most unsatisfactory. The best specialists are those with previous experience of general practice, but these men could certainly not have had previous tropical experience. Also such a system would divide the medical profession abroad into two classes—the acknowledged specialists, many of them young, and those without hope of acknowledgment, whatever their experience and qualities.

For these reasons a statutory entry in the *Register* should not require any domiciliary condition. It should be obtainable by all registered practitioners, whose sole qualifications should be experience, postgraduate qualifications, and practice of the specialty concerned. These can be acquired in the normal course of a medical career in the Tropics by progressive men, who would not need or ask any relaxation of standard for their recognition.—I am, etc.,

C.M.F. GEORGE MACDONALD.

Mental Health Service

SIR,—In reply to the letter under the heading "Asylum Doctors' Pay" it may be stated that the question of salaries and conditions of service of the medical staff in the mental health service is by no means being overlooked. Some useful preliminary work has been done in conjunction with the Medical Superintendents Society, and it is hoped that at the forthcoming annual meeting of the Royal Medico-Psychological Association (Nov. 29) a small but representative committee may be appointed to draw up recommendations. The matter, looked at with regard to the future, is not devoid of complications—e.g., employment of house officers, grading of specialists, extramural duties, etc.—but it is well recognized that an equitable scale of salaries is overdue.—I am, etc.,

W. GORDON MASEFIELD,
Honorary General Secretary, Royal Medico-Psychological Association.

11, Chandos Street, Cavendish Square, W.

The Services

Surg. Lieut. J. M. Couchman, R.N., has been awarded the D.S.C., and Temp. Surg. Lieuts. A. C. Smith and T. A. M. Johns, R.N.V.R., have been mentioned in dispatches for distinguished services in operations, carried out in the face of determined opposition from the enemy, which led to the capture of the Island of Elba.

Temp. Surg. Lieut.-Cmdr. J. W. Buchanan has been mentioned in dispatches for good services to the wounded.

Capt. (Acting Major) S. H. A. Gardezi, M.C., I.M.S., has been mentioned in dispatches in recognition of gallant and distinguished services in Sicily.

CASUALTIES IN THE MEDICAL SERVICES

Wounded.—Capt. P. N. Swift, I.M.S.

Missing at Arnhem.—Capt. C. E. C. Wells, R.A.M.C.

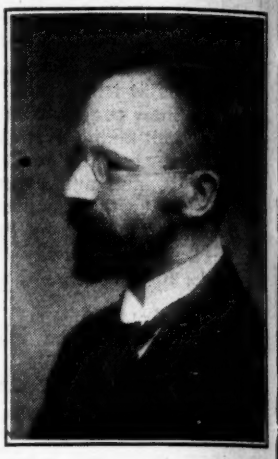
Missing, presumed killed.—Surg. Lieut. Robert Frederick Barlow, R.N.

Reported missing, now reported prisoner of war.—Capt. J. Rutherford, M.C., R.A.M.C.

Obituary

RAYMOND JOHNSON, O.B.E., F.R.C.S.

Raymond Johnson, consulting surgeon to University College Hospital, died in his sleep in his 83rd year. Entering University College in 1881 as an Exhibitioner he very soon showed his mettle, and by the time he had completed his clinical studies at University College Hospital he was the holder of three gold and six silver medals. In 1886 he added to these by winning two gold medals in the London M.B. He then started seriously on his surgical career by becoming a demonstrator of anatomy before taking the Fellowship of the Royal College of Surgeons in 1888. Four years later he was appointed to the staff of University College Hospital, where he remained for 31 years, retiring before his time in 1923 because he feared that he was standing in the way of his colleagues, who at that time were committed to retirement at the age of 60. He retained his active connexion with the Royal College of Surgeons until 1926, when he finally gave up his professional interests after serving on the Council of the College for eight years and as a member of the Court of Examiners for nine years. At various times he also acted as examiner for the Universities of Birmingham, Cambridge, London, and Leeds.



Raymond Johnson had no doubts as to his place in the profession he had chosen. He had no desire to pose as a research worker or even to lay claim to a great deal of original work. He was content, as well he might have been, with the reputation which he attained as an eminently sound consultant, a skilful surgeon, a lucid teacher, and an ideal colleague. Yet it would have surprised him to know how vividly he is remembered to-day by those who knew him well. His character was in fact a rare one, for he combined with a gentle and rather retiring disposition a surprisingly wide knowledge of human nature and a comprehensive tolerance for its failings. His standards of conduct were very high, but they were for himself, and if others did not live up to them Raymond Johnson would always be their friend but never their judge. His apparent meekness could disappear in a flash when defending the rights of others, and he could be positively disingenuous when occasion arose to cover the faults of his colleagues or his juniors.

Two wars interrupted his career, for he served as surgeon to the Imperial Yeomanry Hospital in the South African War, and again in 1914–18, first as a surgeon rear-admiral, and later, when his naval appointment promised to provide more honours than work, as a captain in the R.A.M.C. Then, as always, he considered first and last his own standards. It would not be true to say that honours meant nothing to him, but they would not have been sweet unless by his own standards they were deserved.

It is good to think that Raymond Johnson, who always preferred gentleness, had twenty years of great happiness after his retirement, enjoying his country home, which he shared with his wife and two daughters. A. J. G.

GREVILLE MACDONALD, M.D.

Dr. Greville MacDonald, consulting physician for diseases of the throat, King's College Hospital, emeritus professor of King's College, London, and formerly physician to the Throat Hospital, Golden Square, died at Haslemere on Nov. 3.

Greville Matheson MacDonald was born in Manchester on Jan. 20, 1856, eldest son of George MacDonald, LL.D., poet and novelist. Brought up in a literary and musical home he met as a child many leading writers of the day, and after

leaving King's College School, London, he went with his father to the United States in 1872 and there was introduced to Whittier, Longfellow, Oliver Wendell Holmes, and Emerson. He entered King's College as a medical student and won scholarships there, and graduated M.B.Lond. in 1877, with honours in materia medica and pharmaceutical chemistry. During his clinical course at the hospital he became one of Lord Lister's clerks. Greville MacDonald's career in laryngology began as R.M.O. to the Hospital for Diseases of the Throat in 1886, and he was appointed physician soon afterwards. At King's College Hospital he served as throat physician and lecturer on diseases of the throat and nose from 1893 to 1906, when he retired from the active staff and was elected consulting physician. Between qualification and launching out as a specialist he had earned a living in turn as a ship surgeon, as medical officer to a private asylum, and as a doctor in private practice in Florence. His appointment to the Golden Square Hospital was due in the main to an introduction by Sir Morell Mackenzie, whose private work in London he looked after when Morell was in attendance on the Emperor Frederick at San Remo and Charlottenburg.

Greville MacDonald acquired a large practice and ranked high as a lecturer in his specialty; he was vice-president of the Section of Laryngology at the Annual Meeting of the B.M.A. in 1895 and president at the Montreal Meeting two years later. His foreign honours included corresponding membership of the Société Française d'Otologie, de Rhinologie, et de Laryngologie, and corresponding Fellowship of the American Laryngological Association. Among his medical publications were *A Treatise on Diseases of the Nose and its Accessory Cavities* (2nd edition, 1892) and *Hay Fever and Asthma* (1893). From boyhood he had had many interests outside medicine, and he wrote a number of philosophical essays and romances and studies in human personality. He wrote a life of his father and mother in 1924, and *Reminiscences of a Specialist* in 1932.

Dr. FREDERICK WALKER, formerly chairman of the Holland Division of the British Medical Association, died at Holbeach, Lincs, on Oct. 23. He was born at Wakefield on July 27, 1871, and studied medicine at Leeds, taking the English Conjoint diplomas in 1894. A year later he became senior house-physician and anaesthetist at the Infirmary at Leeds and then practised at Wakefield, where he was assistant honorary surgeon to the Clayton Hospital. He moved later to Holbeach and was appointed medical officer to the Holbeach Institution, the Lincolnshire Joint Board for Mental Defectives, and the Isolation Hospital at Fleet; he was also deputy coroner for the Spalding district. Dr. Walker joined the B.M.A. in 1896, and in recent years was chairman of the Local War Emergency Committee.

We regret to announce the death of Dr. JAMES ALEXANDER DAVIDSON of Montpelier Avenue, Ealing, W.5, on Oct. 27, at the age of 61. He was born in Aberdeen, and graduated M.B., Ch.B. at Aberdeen University in 1907 and M.D. in 1909. He was assistant casualty medical officer at Great Ormond Street Children's Hospital. In 1909 he started his practice in Hanwell, and in 1929 he moved to Ealing, and had practised in Hanwell and Ealing for the past thirty-five years. He became medical officer to the L.C.C. residential schools (which work he enjoyed more than any other) and medical officer to the Hanwell Cottage Hospital. In the last war he was a captain in the R.A.M.C. and medical officer to a British auxiliary hospital in Belgrade. After the war he was appointed medical referee for the Mental Treatments Act, 1920, and more recently medical officer to the Associated Equipment Company. During this war Dr. Davidson served as medical officer to the Middlesex Battalion Home Guard and physician and chairman of the Medical Recruiting Board. He had been a member of the B.M.A. since 1911, was secretary of the Ealing Division in 1922, and chairman of the West Middlesex Division in 1933–4, representing the latter at three Annual Meetings. He was also a member of the Harveian Society. The following appreciation comes from a former partner: Dr. J. A. Davidson was a conscientious and painstaking physician, thorough, calm, and possessing that power which inspires patients with both confidence and assurance. Constantly keeping in touch with current medical literature he was always familiar with the latest methods of treatment. He was a sound diagnostician, dogmatic but willing to see both sides of a question. Dr. Davidson was a dearly loved friend to both young and old, and his passing leaves a gap which cannot be filled.

Universities and Colleges

UNIVERSITY OF LONDON

Sir Ernest Graham-Little, M.P., has been elected chairman of the Council for External Students of London University for the year 1944–5.

LONDON HOSPITAL MEDICAL COLLEGE

The subject for the next award of the Hutchinson Triennial Prize is "The Value of Local Chemotherapy in the Treatment of Wounds." Every candidate must be a full student of the London Hospital, but not necessarily of the Medical College. He may be qualified, and he is eligible to compete until the expiration of ten years from the date of registration as a student of the hospital. Dissertations must be delivered by Oct. 31, 1947. A printed copy of the conditions may be had from the Secretary of the London Hospital Medical Council, Whitechapel, E.

UNIVERSITY OF GLASGOW

Four illustrated lectures on the evolution of social medicine will be given by Dr. Douglas Guthrie in the Zoology Lecture Room of the University on Mondays and Thursdays, Nov. 27 and 30, and December 4 and 7. The lectures are open to members of the University staff, students, and medical practitioners.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

The following candidates were successful in the recent Primary Fellowship Examination:

W. P. Cleland, T. H. Cullen, J. S. Davidson, E. W. Grahame, J. D. Green, J. W. P. Gummer, J. D. Hallissy, H. O. Jones, P. F. Milling, M. R. Milne, M. R. Rifaat, J. M. Sanderson, D. W Thomas, Jean K. M. C. Wilson, W. K. Yeates.

Medical Notes in Parliament

Penicillin Supplies

Mr. KENDALL on Nov. 2 raised the question of penicillin. He said Britain, regrettably, had not started producing this drug until recently. A factory costing £1,000,000 had begun operations that day.

Mr. PEAT (Joint Parliamentary Secretary to the Ministry of Supply) intervened to say that was a Press mis-statement.

Mr. KENDALL said all information on the manufacture of penicillin and of treatment by it had been given to the United States of America, which had done a wonderful job producing it. This production to-day was some 1,200,000,000,000 Oxford units per annum. The supplies they had sent over here represented about 200,000,000,000 Oxford units. Many of our Service men were treated with the drug, which was obtained under Lend-Lease from America. He understood that Germany had been given all the information regarding production of penicillin. Proceeding, Mr. Kendall said bacterial endocarditis was a disease which hitherto had been fatal. Without this drug there was no hope at all. With it lives had been saved here and in the United States. Young people had already been helped in Middlesbrough and Manchester by penicillin. He asked the Ministry of Health to take regionally the few similar cases that would come along. There had not been more than 30 letters asking M.P.s for help. This, Mr. Kendall said, would relieve him from having to try to get penicillin. He neither manufactured nor purchased, but had been allowed to have 4,000,000 or 5,000,000 Oxford units. By regional control the Minister could get doctors trained, through his experts, in the use of penicillin.

Mr. WILLINK said the matter was of great importance. He was anxious to relieve the anxiety of those who believed there had been undue rigidity or inhumanity in the administration of the supplies. In 1941, 1942, and 1943 the resources of America in penicillin had been hardly less strained than our own. From the beginning of this year, owing to the American supplies provided under Lend-Lease for the armed Forces and civilian air-raid casualties—those were the terms—the Ministry had been able to do a lot for those two classes of people. In the early part of 1944 it became clear that during that vital summer the total supplies, home-produced and imported, would probably be more than sufficient for the needs of the armed Forces. The first allocation for clinical trials under the control of the Clinical Trials Committee of the Medical Research Council had been in January, 1944. By August, 1944, the Ministry was able to provide a general supply on a very restricted basis for the use of civilians. In the three subsequent

months the amount hoped for in August had been maintained. He took responsibility for the arrangements made. The allocation was on a regional basis.

The decision on how that allocation should be used, Mr. Willink continued, was made by the university medical schools. Each school had set up its expert committee. Treatment was given in teaching hospitals and in other hospitals which had been approved for that purpose. Penicillin was not a drug which could be used with advantage in every type of disease. In some it might be the only means of saving life; in others an alternative to sulphonamides; in others it might be ineffective. Some doctors even asked for penicillin for use in cancer, mycosis fungoides, and chronic leukaemia, in which it was quite ineffective. It was only suitable in cases which were treated in a hospital or nursing home under continuous medical supervision. In an address last month Prof. Henry Cohen had said that doctors should deprecate public clamour by responsible and influential persons for the use of penicillin in an isolated case where large amounts might be necessary in treatment and where results were extremely doubtful, at the expense, perhaps, of several cases in which the use of penicillin would almost certainly turn the balance in the patient's favour. Advice issued by the Ministry of Health, based on that of a committee of experts from many fields, was contained in a memorandum on the conditions in which penicillin should be used and in others for which it should not be used. Recommended as prima facie suitable for treatment by penicillin were staphylococcal infections. These included septicaemia, early acute osteomyelitis, severe carbuncle, cavernous sinus thrombosis, or any other life-endangering infection. The second class for which use was recommended were haemolytic streptococcal, pneumococcal, and meningococcal infections and any life-endangering infection of the type which had failed to respond to adequate sulphonamide treatment. The third class was gas gangrene. It was, however, recommended that penicillin should not be used for rheumatic fever, ulcerative colitis or other intestinal infections, bacterial endocarditis, or syphilis. Reports from the hospitals indicated that supplies had proved sufficient for all suitable cases in the first group. There was no satisfying evidence at present on the effect of penicillin in the treatment of bacterial endocarditis. Some believed that if a patient seriously ill with this disease was given large doses he would show an immediate improvement, but that the condition would probably lapse and that more penicillin must be given. There was not yet evidence to show whether by continued treatment the patient could be definitely cured or kept alive. Mr. Willink announced that it was proposed to investigate the effects of penicillin on this disease and to see whether a method of application could be devised which was likely to be successful. The quantities allotted to his Department were being progressively increased. By January there would be twice as much available for civilian use as there was to-day. It would be wrong to use penicillin for our civilian population on a more lavish basis than the United States used it for theirs. Before the end of 1945 the penicillin available would meet all, or nearly all reasonable demands.

Planning for Social Security

Sir WILLIAM JOWITT on Nov. 2 asked the House to approve the intention of the Government, as declared in the recent White Paper, to establish an enlarged and unified scheme of social insurance and a system of family allowances. He said the Government had addressed itself in an effective manner to an intricate job. In the main the proposals were not new. Social insurance had long been an essential feature of the national life. The time had come for improvement of existing benefits and for the introduction of new ones on the lines of bringing everyone into the new scheme and of welding fragments into a comprehensive whole. The benefits were calculated actuarially, and the taxpayer would pay one-sixth of the various benefits, except for unemployment insurance, where he pays to-day and is to pay in future one-third. He would not pay toward the death grant, but would pay the whole cost of family allowances. The Government thought that the State should help parents to discharge their responsibility. They proposed that all pupils attending primary and secondary schools under the Education Department should receive, free of cost to the parent, school meals and milk up to the age of 16. Discussing the proposals for old age pensions, Sir William said that at present there were 16 persons over the retirement age to 100 contributors. In 30 years there would be 31. The cost would increase by £155,000,000. That was on the assumption that fertility and death rates would remain as to-day. If our medical services should improve and cures be found for some killing diseases, those figures would be falsified. The net result of the whole social scheme was that in the first year the taxpayer or the ratepayer would bear 54% of the entire cost. By 1975 he would bear 67%.

Mr. GREENWOOD recalled that a few months ago the House had discussed a national health scheme. That was an essential part of the plan. There was still an enormous amount of preventable disease. He hoped the House would bring that fully into the picture at a later stage. Mr. JOHN GRIMSTON regretted that the scheme had been made compulsory. Many people had a conscientious objection to using a doctor. He objected to paying a death benefit of £20. The sole result would be to put up the cost of funerals. He objected to the abolition of the friendly societies, which had adequate arrangements for medical referees and sick visiting.

When the debate was resumed on Nov. 3 Mr. BUTLER said the Government had a positive policy for the young, partly included in the new Education Act. There were also additional benefits under the health plan and under this insurance plan. The Government was spending £57,000,000 of public money on cash allowances for children, excluding the first child, and £60,000,000 on free milk and meals at school. The family was expected to maintain the first child. Family allowances helped to take the strain where the number of children created an insufficiency injurious to health. The Government hoped that family allowances would result in an increase in the birth rate. But confidence made the birth rate rise and the plan as a whole would give greater confidence to our families. If a child entered hospital there would be no charge on the parents under the provisions of the school medical service, but the parents would continue to receive the family allowance. Despite the difficulties of the war the number of children taking their midday meal at school had risen in the last three years from 300,000 to 1,600,000. Little short of 14,000 canteens had been provided to serve 19,000 out of 28,000 schools. Milk had been provided in 27,000 schools. For the "under-fives" the Government would continue for the time being the national milk scheme and the provision of orange juice, cod-liver oil, etc., which had been part of the wartime plan. The Government could not pledge itself to continue the scheme after the war in exactly the same form as now. It asked for time to consider how the needs of the "under-fives" and of nursing and expectant mothers should be met when liquid milk was freely available. Provision in kind would ultimately cover the whole child population. The Government was convinced that it was impossible within the new unified scheme to use approved societies administering only the National Health Insurance part of the scheme.

Sir WILLIAM BEVERIDGE begged the Government to take as its primary aim the elimination of want among children. Col. ELLIOT said a survey carried out in London last June by Lady Mellanby of the teeth of London school-children showed much improvement, which Lady Mellanby attributed largely to the milk scheme of the Milk Marketing Board. The initial work for the scheme had been carried through by the Medical Research Council.

Sir JOHN ANDERSON said that, taking a person "continuously" in employment from 16 to 65 with a normal expectation of life when he retired, 12% of his life from 16 would be spent in sickness or unemployment and during 11% he would draw pension. He added that the Government intended to do its best to ensure that employment in connexion with the new scheme, so far as they were qualified, was provided for full-time officers of approved societies.

The House carried a motion approving the Government's intentions.

Medical News

Sir Joseph Barcroft will give a lecture on "Food and Processing —The Nutritive Value of Processed Food" at a meeting of the Food Education Society on Monday next (Nov. 20) at 2.30 p.m. in the Conference Hall of the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.

A meeting of the Scottish Group of the Association of Industrial Medical Officers will be held on Wednesday, Nov. 22, at 3 p.m., in the Institute of Hygiene, University of Glasgow. Prof. Ferguson will give an address on the resettlement of disabled persons in industry. Time will be allowed for discussion. Members may bring friends, and those interested in industry are invited to attend.

At the meeting of the Section of Epidemiology and State Medicine of the Royal Society of Medicine on Friday, Nov. 24, at 3 p.m. Sir Leonard Rogers will read a paper on "Smallpox—Incidence and Vaccination in India." The discussion will be opened by Dr. C. Killick Millard.

At a meeting of the Colour Group of the Physical Society on Wednesday, Nov. 22, at 3.30 p.m. in the Physics Department of the Imperial College, Imperial Institute Road, S.W.7, Mr. E. Willmer of the Cambridge Physiological Laboratory will read a paper on "Retinal Structure and Colour Vision." The spectral sensitivities of the rods and the cones in the human eye, their neural connexions, their phylogenetic and ontogenetic development, their behaviour, and their varieties will be discussed in relation to a hypothesis that human colour vision is primarily due to the relative performance of these photo-receptors and not to the performance of the cones only. The peculiar properties of the so-called red-free area of the fovea centralis will be examined and the general hypothesis will be considered in relation to the essentially trichromatic basis for colour vision. An informal discussion will follow the paper.

The 103rd annual meeting of the Royal Medico-Psychological Association will be held on Wednesday, Nov. 29, at 11, Chandos Street, Cavendish Square, W., under the presidency of Lieut.-Col. A. A. W. Petrie, M.D., F.R.C.P. On the previous day the council and committees will meet at the same address.

Durham University has decided to open the vacant whole-time professorship of surgery at King's College, Newcastle-upon-Tyne, to candidates serving in H.M. Forces. This enlightened decision was made after consultation with the Director-General, Army Medical Services. The salary of the chair is £2,000 a year, and Dec. 31, 1944, has been given as the preliminary date by which applications should be received. The University will not, however, fill the appointment until it is satisfied that persons serving over-seas have had full opportunity to apply. If the successful applicant is on national service, he will not be required to take up his duties until his release from such service. Applications should be made to the Acting Registrar, University Office, 46, North Bailey, Durham.

Dr. George Walker Hinchliff of Dover has been commended for brave conduct when attending to wounded under shell-fire.

EPIDEMIOLOGICAL NOTES

Discussion of Table

In *England and Wales* the incidence of measles, scarlet fever, and whooping-cough continued to rise, there being reported respectively 663, 112, and 91 more cases than last week. Returns for acute pneumonia fell by 102, for dysentery by 29, and for diphtheria by 26.

Yorks West Riding reported 40 more cases of scarlet fever than last week. The greatest increase in measles was in the north, especially in Lancashire, where returns rose by 267; in Yorks West Riding they went up by 66, in Staffordshire by 63, in Durham by 53, in Northumberland by 44, and in Glamorganshire by 41. In contrast to the general trend, Devonshire had 72 fewer cases than last week, and Cheshire 59.

The notifications of dysentery, 362, fell by 29. The largest returns were Lancashire 53, Glamorganshire 41, London 38, Essex 31, Suffolk 29, Yorks East Riding 29, Hertfordshire 19, Surrey 16, Gloucestershire 15.

In *Scotland* there were 56 more cases of measles than last week, and 29 more of diphtheria. During the recent outbreak of gastro-enteritis among infants in Glasgow there were 296 deaths during the eleven weeks from mid-August to mid-October. No specific factor causing the epidemic has been found.

In *Eire* notifications of diphtheria fell by 25, but were still high—128 cases.

In *Northern Ireland* scarlet fever rose by 23 cases after the large fall of 46 in the preceding week.

Diphtheria

According to returns received from all but a few local authorities in England and Wales the number of notifications of diphtheria in 1943 among immunized children was approximately 5,050. According to the same returns, of 1,079 children who died from diphtheria in 1943, 42 had been immunized at some time. In the two years 1942–3 the annual rate of incidence of diphtheria among immunized children, based on the estimated time of exposure to risk, was rather more than a quarter of that among those not immunized, and the corresponding mortality ratio was about 1 to 23.

The returns received from medical officers of health in Scotland show that the number of immunized children under age 15 who developed diphtheria during the first six months of 1944 was 827. The information at present available shows that 2 immunized children died during the period.

Week Ending November 4

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 2,149, whooping-cough 1,135, diphtheria 633, measles 4,827, acute pneumonia 520, cerebrospinal fever 42, dysentery 256, paratyphoid 3, typhoid 5, poliomyelitis 14.

No. 43

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended Oct. 28.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1944 (a)	(b)	(c)	(d)	(e)	1943 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	47	4	15	3	3	26	3	21	1	—
Deaths		—	1				—	—		
Diphtheria	554	9	204	128	25	702	39	166	101	33
Deaths	8	1	2	2	—	21	1	5	3	—
Dysentery	362	38	101	—	—	248	54	66	2	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	3	—	—	—	—	—	—	—	—	—
Deaths		—					—			
Erysipelas			56	14	—			67	6	4
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				37					59	
Deaths	37	2	13	18	7	55	4	17	12	5
Measles*	4,442	65	309	30	99	585	49	74	27	2
Deaths	3	—	1	—	—	2	1	—	—	—
Ophthalmia neonatorum	64	3	19	—	—	75	6	19	—	—
Deaths										
Paratyphoid fever	14	—	1 (B)	—	—	5	—	2	—	—
Deaths	—	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal†	538	32	10	2	2	576	53	21	1	10
Deaths (from influenza)	17	1	1	—	—	25	4	14	3	2
Pneumonia, primary			178	26				258	21	
Deaths		23		10	8		24		9	10
Polio-encephalitis, acute	1	—				1	—			
Deaths		—					—			
Poliomyelitis, acute	14	—	1	—	—	13	1	2	3	1
Deaths		—					—			
Puerperal fever		7	15		—		4	18		—
Deaths							—			
Puerperal pyrexia‡	162	10	10	1	1	196	11	14	1	5
Deaths		—								
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	2,288	60	325	51	82	3,623	276	412	50	109
Deaths	2	2	—	—	—	1	1	—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	9	—	1	7	2	7	—	3	6	—
Deaths	—	—	—	—	—	2	—	—	1	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	1,061	52	76	20	10	1,693	105	205	12	16
Deaths	7	1	—	1	—	3	2	5	2	—
Deaths (0–1 year)	342	19	55	40	31	304	32	68	43	15
Infant mortality rate (per 1,000 live births)										
Deaths (excluding stillbirths)	4,279	589	551	182	132	4,287	678	596	197	126
Annual death rate (per 1,000 persons living)			12·7	11·8	§			13·4	13·0	§
Live births	6,728	508	983	361	250	5,822	704	879	336	259
Annual rate per 1,000 persons living			20·0	23·4	§			17·9	22·1	§
Stillbirths	197	13	29			208	20	41		
Rate per 1,000 total births (including stillborn)			29					45		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

‡ Includes puerperal fever for England and Wales and Eire.

§ Owing to evacuation schemes and other movements of population, birth and death rates for Northern Ireland are no longer available.

Letters, Notes, and Answers

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ANY QUESTIONS?

Water Testing

Q.—*Can you kindly explain how the same water can give such different results as the following?*

E.P.H.L.S.	Probable Number of Coliform Bacilli
15/12/43	0
15/8/44	8
15/8/44	70
15/9/44	350
18/10/44	110 (A)
18/10/44	250 (B)
Dr. A. 15/9/44	0
Dr. B. 2/10/44	0

What am I to infer? I have advised it to be boiled. (All samples were collected by the water engineer in sterile (?) bottles supplied by the laboratories.)

A.—The bald inference from the data submitted is that the water supply is unsafe and the questioner's action in advising boiling is justified. This, however, can be only a temporary measure, and the conditions require close investigation. In this connexion it should be made clear (1) whether the samples are of water at the tap or at some other stage before delivery; (2) whether samples from E.P.H.L.S. 15/9/44 and Dr. A. of the same date were taken by the same person and at the same place; (3) whether the sampling officer's procedure is such as to preclude contamination after the sterile bottle leaves the laboratory; and (4) as to the weather conditions at the several dates, especially as regards flooding. The discrepancy between the reports on samples A and B collected 18/10/44 is not of great significance. Before advising his authority on this problem the M.O.H. should discuss these results in detail with the bacteriologist (preferably at the waterworks), who may suggest further experiments to determine what defects exist in the system.

Insulin to Increase Weight

Q.—*Injections of insulin 10 units t.i.d. a.c. over a period of four or five weeks are said to increase the weight of persistently thin individuals (healthy, non-diabetic). Is there any foundation for this belief, and if so, how does insulin bring about such an increase in weight?*

A.—Insulin is sometimes useful in increasing the weight in patients whose appetite is very bad. It does this by producing hypoglycaemia, and it is useless unless pressed to this point. Many patients rendered hypoglycaemic become ravenously hungry and therefore eat more. Unfortunately the method often fails, sometimes because the patient still lacks appetite despite hypoglycaemia and sometimes because the increased intake of food does not cause a gain in weight.

Tests for Liver Function

Q.—*What are the best tests of liver function? How are they applied and the results interpreted?*

A.—The choice of suitable tests depends upon the clinical material and the facilities available. The serum bilirubin estimation, urinary tests for urobilin(ogen), and the hippuric acid test are the easiest to perform and will often give useful results, particularly in non-jaundiced patients. They will rarely distinguish between obstructive and non-obstructive jaundice, for which purpose more help may be obtained from the flocculation tests—e.g., the serum-colloidal-gold reaction and the cephalin-cholesterol test—the serum alkaline phosphatase, modern versions of the galactose-tolerance test using blood-galactose estimation, or the serum-protein determination. It is impossible to deal here with technical details, which are described in current articles and textbooks. Two recent numbers of this *Journal* contain accounts of most of the tests mentioned. (Feb. 12, 1944, p. 211, and Sept. 16, 1944, p. 363.)

The interpretation of results needs care because of the possibility of secondary liver involvement in various diseases such as heart failure, acute and chronic infections, anaemias, and hyperthyroidism. In general it may be said that a suitable combination of tests will materially assist the clinician in the diagnosis of liver disease and in the differentiation of the various types of jaundice. Thus in jaundice due to hepatitis or cirrhosis the flocculation tests are usually positive, the phosphatase moderately raised, galactose tolerance impaired, and the serum globulin may be raised. In obstructive jaundice the flocculation tests are usually negative, the phosphatase much higher, and galactose tolerance and serum globulin may be normal. In subacute and chronic hepatitis the serum albumin has prognostic significance, very low values indicating a poor outlook.

Bacterial Enteritis

Q.—*We recognize infections of the air passages and call them by the names of the parts affected—e.g., bronchitis. Is there any fundamental reason why parts of the gut—e.g., the colon—should not be similarly the seat of infection? Yet physicians generally doubt such a diagnosis as streptococcal colitis. I know a doctor who developed acute diarrhoea during an epidemic of what G.P.s called gastric flu. But his diarrhoea continued for thirteen months, then stopped. His weight fell, and after a few weeks he sought advice—? neoplasm or other serious cause. Radiological investigation showed an exceptionally hyperactive stomach and long spasmodic contractions in the colon, which was lacking in normal haustrations. A barium meal was voided in less than five hours' time. Examinations of the stools showed large numbers of bacteria, mostly Strep. viridans. The percentage of these varied from 80 to 10 and roughly corresponded with the severity of the diarrhoea. Sulphaguanidine was helpful but not curative. One physician's diagnosis of streptococcal colitis was negatived by another's of anxiety neurosis. But the latter seemed to be secondary to the bowel upset and the uncertainty of its cause.*

A.—Of course enteritis occurs from bacterial infection—as, for example, tuberculosis, typhoid, and cholera—and pathologists recognize a type due to the streptococcus. To diagnose such a lesion one would require not merely the presence of bacteria in the stools but also signs of inflammation—red blood cells, white cells, a positive test for occult blood, and albuminoid secretion in the stools, together with general phenomena such as fever, leucocytosis, and a raised erythrocyte sedimentation rate. The difficulty about the findings in the present case is that *Strep. viridans* is only feebly pathogenic and is generally supposed to be a mere transient which has been swallowed from foci in the mouth and nasopharynx. The numbers surviving depend largely on the pabulum provided and the rate of passage through the alimentary tract. The number of streptococci in cultures from stools may therefore vary directly with the severity of a diarrhoea, without their having any aetiological connexion with it, and this is probably what is happening in the present case. In the absence of the other signs of infection a diagnosis of enteritis is not justified, and the condition should be treated as a disturbance of motility. Such disturbances are often severe and intractable. Is there any fundamental reason, in fact, why disturbances of intestinal motility should be any less serious than disturbances of cardiac motility?

Intravenous Anaesthetics

Q.—*I notice that all references to intravenous anaesthesia for a considerable time have specified pentothal. I have always used soluble hexobarbitone under various proprietary names, and have found it quite satisfactory. Will you please say if you consider that pentothal has any definite advantage over soluble hexobarbitone.*

A.—Safe general anaesthesia is largely a matter of muscular relaxation achieved at the expense of little respiratory depression. Many consider that pentothal is better than hexobarbitone because it gives a given degree of muscular relaxation with less respiratory depression. Weight for weight pentothal is the more powerful drug. Anyone accustomed to use hexobarbitone will find that he gets approximately equal effect by giving only a little more than half the amount of pentothal.

Local Authorities and Dance Halls

Q.—*Are there any regulations relating to ventilation of dance halls and to the number of people allowed in a room of a given size?*

A.—The control of dance halls is a function of the licensing authority, which, in England and Wales, may or may not be a health authority. For instance, in London and the Home Counties it is usually the county council, but elsewhere the justices of the peace are the authority, unless the power has been otherwise allotted by local Act of Parliament. Licences may be granted subject to terms and conditions, which might include reference to ventilation and other sanitary matters. In practice the licensing authority is primarily concerned to ensure that proper order is kept and precautions are taken for the safety of the public, especially as regards fire. Due regard to health questions is more likely to be taken in those places where the chief constable and the medical officer of health have close liaison in preparing reports for the authority. Regulations have been made by the London County Council and could no doubt be obtained by application to the County Clerk, County Hall, London, S.E.1.

Rheumatoid Arthritis and B.S.R.

Q.—Is it correct that in the presence of a normal blood sedimentation rate treatment of rheumatoid arthritis by gold injection will be of no value?

A.—A normal sedimentation rate is so unusual in true rheumatoid arthritis that it rouses a doubt whether the case may not be of different pathology; it is also possible that the disease is no longer active. In either case a careful review of the clinical features must be the guide as to whether gold treatment is indicated, and in view of the possible risks it should be avoided unless there is strong evidence for its use. On the whole it would seem unlikely that gold would be of any service in the case in question; possibly before arriving at a final decision it would be wise to have the test repeated, as many circumstances affect it which may not always operate.

Pre-menstrual Psychology

Q.—What, if any, is the nature of the endocrine imbalance which produces the change in personality of so many women during the seven days preceding menstruation? Many of these patients complain, not of dysmenorrhoea or of any physical discomfort, but of sheer loss of self-control, wickedness, hatefulness, and excessive drive which render life almost intolerable for themselves and for their families. I have tried progesterone during this period and in some cases have followed it, for a few days after menstruation, by oestrogens, but judging by results I may simply be adding fuel to the fire. Is there any means of determining if the anterior lobe of the pituitary is overactive, and if it is so, how can one inhibit its influence? Most alienists insist that the change is purely psychological, but in women whose menstrual type is irregular this week of anxiety definitely begins earlier or later to correspond with the alteration in the time of onset of each period. This would appear to rule out conditioned reflex as a cause.

A.—Mental and physical changes in the pre-menstrual phase have been studied by a number of workers. There is some evidence that disturbances of water balance due to the water-retaining properties of steroid hormones operate unfavourably in individuals of susceptible constitution (Thorn, G. W., Nielson, K. R., Thorn, D. *Endocrinol.*, 1938, **22,** 155). It has been claimed by J. P. Greenhill and S. C. Freed (*J. Amer. med. Ass.*, 1939, **112,** 1573) that relief of pre-menstrual discomfort may be obtained by administration of ammonium chloride to discharge sodium tension and effect an output of water. Both Israel and Schmidt have reported cases in which insufficient production of corpus luteum hormone appears to be associated with severe mental swings in the pre-menstrual phase, and have suggested progesterone as a possible cure (Israel, S. L., *J. Amer. med. Ass.*, 1938, **110,** 1721; Schmidt, H. J., ibid., 1943, **121,** 190). There are certainly several factors involved, and it would be fair to say that an unalterable basic mental constitution is the most important. The extent to which endocrine changes can influence the psychological state is subject to great individual variation. The methods suggested above can be tried, and should prove to be successful where the physical element is the relatively strongest factor. There is obviously no one specific endocrine cure, and no simple functional disturbance of the anterior lobe of the pituitary can be held responsible.

Treatment of an Epileptic

Q.—I should be glad of advice on the treatment of an epileptic girl aged 15 years. She has had fits all her life. They are not very severe; she usually remains unconscious for two or three minutes and has up to three fits a day. She is an intelligent girl and is anxious to become independent of her parents and to earn her own living. For several years she has been on sod. bromid. gr. 15, tinct. bellad. m. 5, t.d.s., together with sod. phenobarbitone gr. 1 b.d., but the fits have never been reduced to below one a day. Phemitone gr. 3 b.d. and sodium diphenyl hydantoinate have also been tried with no better result.

A.—There are some epileptics whose attacks can never be completely controlled by anticonvulsants in any combination, and the dose of bromide and phenobarbitone that this patient is having is approaching the maximum possible. If sodium diphenyl hydantoinate has not been of benefit alone, it would be well to add it to the dose of bromide and phenobarbitone that the patient is having, and after a few days to drop the bromide, because in some cases luminal and epanutin together are of more benefit than a large dose of each alone.

Combining Vitamins

Q.—What are the limits of compatibility of vitamins? Can vitamins A and D be combined in the same mixture with vitamin C or B, using glycerin as a base? By the mixing of the oil- and water-soluble vitamins, is the value lost?

A.—There is very little evidence to suggest that fat-soluble vitamins, which are sometimes rather sensitive to acid conditions, and water-soluble vitamins, some of which are easily decomposed by alkalis, cannot exist together when properly combined at round about neutral *p*H. It is difficult, however, to understand what is meant by "combining" fat-soluble and water-soluble vitamins, "using glycerin as a base." Pure glycerol is a substance in which the fat-soluble vitamins will certainly not dissolve at all, and it seems unlikely, although there is little experimental evidence on the subject, that it would be a particularly good solvent for water-soluble substances. Thus, an attempt to present fat-soluble and water-soluble vitamins in a glycerin base is most likely to lead to a suspension, of more or less fineness, in which both fat-soluble and water-soluble substances are liable to oxidation, and therefore to destruction. This is, however, not incompatibility in the pharmaceutical sense as usually understood. If the question refers to physiological compatibility, it is hardly sufficient to refer to the fact that all the vitamins occurring in food appear to be effective in the presence of one another. Mixtures of synthetic vitamins might quite well behave differently. Evidence that they do is non-existent or at best inconclusive. There are good grounds for accepting the fact that the importance of vitamin E in human nutrition is at least in part due to its anti-oxidant protective action on the β-carotene in the diet; there are also curious reactions between the water-soluble vitamins, probably associated with the fact that we depend to some extent for some of these substances on our gastro-intestinal flora, the nature of which is, in turn, determined by the nutrients in our, the host's, diet. These are causes of compatibility, rather than the opposite. In general, much the best procedure, if it is desired to prepare some multi-vitamin product, is to study the survival therein of the individual constituents by recognized and approved methods, under various conditions of storage, and not to use (or market) such a product until satisfactory proof has been obtained for the stability of all those constituents. Indeed, the recent Pharmacy Act and food-labelling regulations now make it necessary to proceed in this way, whether for medicinal or food products.

Sodium Morrhuate for Ganglion

Q.—Is the treatment of a ganglion with sodium morrhuate or other solution a reliable cure? What is the exact method of using these solutions in this condition?

A.—There is no absolutely reliable cure for a ganglion. Rupture by pressure, evacuation after puncture by a tenotome, injection of a solution of sodium morrhuate, and excision are all recognized methods of treatment. Any of these methods may cure; none can be guaranteed to cure. Excision gives the best chance. The technique for injection of sodium morrhuate is as follows. The skin over the ganglion is sterilized and anaesthetized by local injection of 1% novocain. A large-bore needle is inserted into the ganglion, the contents expressed, and then half a cubic centimetre of a 5% solution of sodium morrhuate injected; the needle is then withdrawn and a sterile dressing applied. The reaction is sometimes unpleasant, but cure has been known to follow.

Penicillin and Poliomyelitis

Q.—I have had an inquiry regarding the possible use of vivicillin in late infantile paralysis, and the assertion was made that there was a recorded case of cure and recovery of function. Can you corroborate or refute this, and is there any evidence to show that vivicillin or penicillin is of any avail in the treatment of the sequelae of infantile paralysis?

A.—It is inconceivable that any chemotherapeutic agent could be of benefit in "late" infantile paralysis—i.e., after the infection has done its damage. It is improbable that penicillin would have any effect even in the acute stage: virus diseases in general are insusceptible to penicillin, the only evidence to the contrary of which we know being experiments by Heilman and Herrell (vide *B.M.J.*, July 15, 1944, p. 85) showing an effect on ornithosis. We are at a loss to understand how the suggestion that vivicillin is of any use for this purpose can have gained currency. The only report on this material which has appeared in a regular medical journal (T. Crawford, R. S. Handley, and W. H. Hargreaves, *Lancet*, June 3, 1944, p. 738) was to the effect that it failed to cure any of 12 cases treated, although they were suffering from conditions due to penicillin-sensitive organisms.

Pethidine

Q.—Pethidine is a drug new to most medical men. What are its uses and abuses? What are the appropriate doses? Is it habit-forming, or are people said to have become addicted to it, probably of the type who would abuse almost anything—e.g., alcohol, tea, tobacco, etc.? Would it be indicated for spasmodic contractions of the stomach and colon (as shown by screening and x-ray pictures)?

A.—Pethidine is used for relief of pain and the dose is 25 to 50 mg. (about 1/2 to 1 grain) three times daily. Ampoules are available for intravenous or subcutaneous injection, and when given slowly into a vein it is said to produce prompt relief. It is not as effective as morphine but it is more effective than aspirin. Its chief value is that it does not cause nausea or vomiting as morphine does in many people, and so can be used for these patients. It was recently used successfully

in a patient of this kind who was suffering from inoperable carcinoma with secondaries in the spinal column. It seems to be less effective for traumatic than for neuritic pain. It is advocated for spasm of the intestinal tract and urogenital system, and is described as a spasmolytic as well as an analgesic. It is probably a habit-forming drug, though to a less extent than morphine or even codeine.

Effects of Stilboestrol

Q.—*Does the administration of stilboestrol stimulate the adrenals and the hypophysis cerebri, causing increased blood pressure, vertigo, and other disturbances resembling the symptoms of arteriosclerosis?*

A.—In small animals stilboestrol administered in large doses may produce hypertrophy of the adrenal cortex. It appears to inhibit the hypophysis, and large chromophobe adenomas have been produced by continued administration, together with cessation of skeletal growth. In man no evidence of adrenal effect has been clearly indicated, but inhibition of pituitary activity is shown by the diminution or disappearance of gonadotrophins from the urine in menopausal women treated with stilboestrol. Clinically, this results in disappearance of unpleasant vasomotor symptoms, and even a reduction in the increased blood pressure which sometimes occurs at the climacteric. I know of no clinical evidence, and certainly have not observed any, which suggests that "increased blood pressure, vertigo, and other disturbances resembling the symptoms of arteriosclerosis" are ever produced by stilboestrol or other oestrogens as usually administered in woman.

Iron and Constipation

Q.—*Is ferri et ammon. cit. constipating? I have a number of anaemic women who complain they cannot take iron as it makes them feel constipated. What is the remedy?*

A.—The large doses of iron and ammonium citrate which are prescribed nowadays more often produce diarrhoea than constipation, but if constipation does occur it is well to substitute mistura ferri aperiens, *N.W.F.*, which contains ferrous sulphate and sodium sulphate. Freshly prepared Blaud's pill is often well tolerated, and if this also fails, colloidal iron may be given in the form of liquor ferri dialysatus, *B.P.C.*, or one of several similar proprietary preparations.

Xerodermia

Q.—*A young woman who has always suffered from xerodermia has one child of about 2 years of age. During pregnancy the skin became almost normal, but now is as bad as ever, and in addition she now gets severe chilblains, deep, painful cracks on the plantar surface of her heels, and swelling of her ankles and legs, especially if she walks any distance. No cardiac, renal, or other cause can be found for the swelling. Calcium treatment has proved of no value. In view of the improvement during pregnancy, do you consider hormone treatment is indicated and, if so, in what form and dosage? Is any other treatment likely to be of any value, and is friar's balsam the most satisfactory local treatment for these cracks as for cracked fingers?*

A.—It has for long been known that a number of conditions of the skin appear and persist during pregnancy, and that others temporarily clear up, but in our present state of knowledge there are no guiding principles indicating the kind of hormonal treatment suitable for such conditions. Treatment for xerodermia aims at supplying something to counteract the abnormal dryness, such as liquid paraffin, to which a little starch may be added. The painful cracks on the feet call for protection by elastoplast and boric ointment, or possibly friar's balsam. The swelling of the legs and ankles is probably an independent phenomenon arising from other causes.

LETTERS, NOTES, ETC.

Demobilization of Medical Students

Dr. H. STRATFORD COLLINS writes: As you have opened the subject of medical demobilization in your columns, may I raise the question of demobilization of medical students. There must be an appreciable number of them in all branches of the Services at present, and many of them have served for some years. They include students who from high motives have abandoned their studies to serve but who may, after Germany is beaten, be ready and anxious to take them up again. There are also students who had their exemptions withdrawn as their tutors did not consider that they were making satisfactory progress. No standard was laid down for this, and it appears to have varied considerably in different schools and even under different tutors in the same school. Some students, having lost their exemption for failure in an examination, passed it while waiting for their call-up, but were not allowed to continue. These men may be the most high-spirited and least studious of their years, but are not necessarily the worst doctors when qualified. Discipline, service, and experience have probably produced a more serious outlook by now. If they are retained in the Services and sent to the Japanese theatre of war, and the break in their studies is lengthened by two or probably three years, they may well be lost to medicine for good. On qualification, should the war be over, they will be immediately available to help to fill the vacancies in the profession, as they will have completed their compulsory military service. The welfare of these students appears to be nobody's business. They do not seem to be under the jurisdiction of the Central War Board, and are left entirely to the tender mercy of the Ministry of Labour.

Diagnosis of Minimal Hyperthyroidism

Dr. E. C. H. HUDDY (Truro, Cornwall) writes: The reply to the first question in "Any Questions?" in the *Journal* of Nov. 4 raises a point which is continually giving rise to difficulty—namely, the diagnosis of mild cases of hyperthyroidism. In this connexion the work of J. D. Robertson does not seem to have attracted the attention that it deserves. Quite apart from his demonstration of the fact that the estimation of basal metabolism in ambulant patients is, subject to certain conditions, a perfectly satisfactory procedure (*Journal*, May 6, 1944, p. 617; and see also the impressive letter from I. M. Rabinowitch of Montreal in the *Journal* of July 29 last), he points out that *the response of the basal metabolic rate to the administration of iodine* constitutes a specific test of very great value in the diagnosis of cases of minimal hyperthyroidism. Robertson refers to one patient with hyperthyroidism who had a B.M.R. of minus 8 falling to minus 27 after administration of iodine, and another such patient in whom these figures were respectively minus 2 and minus 15. He points out also (*Practitioner*, Dec., 1935) that the B.M.R. (subject to certain conditions) is remarkably constant for a given normal individual; the "error" of the B.M.R. is often referred to, but this should apply to the differences between the rates of normal individuals, not the differences between rates given by the same normal person at different times. Admittedly, a high proportion of cases of hyperthyroidism can be diagnosed on clinical grounds alone, but it would appear that the response of the B.M.R. to iodine should be used far more widely than it now is in cases of *minimal* hyperthyroidism, particularly in those worrying diagnostic problems which are presented by such minimal hypersecretion in women of middle age whose symptoms are cardiac.

In regard to technique, the papers referred to repay close study. The answer to your "question" states that "we have no test for thyroid function." I would suggest that the response of the B.M.R. to iodine may fairly claim to be such a test, for, as Robertson states, the "normal" rate shows no change after iodine, but in hyperthyroidism iodine produces almost invariably a significant fall (rarely a rise) in metabolic rate, and Plummer's demonstration of the value of iodine as pre-operative preparation for subtotal thyroidectomy incorporates this essential fact. Of course, the patient with hyperthyroidism generally responds to iodine with a fall in pulse rate, but this test is not infrequently vitiated by the existence of auricular fibrillation. Consideration of the result of a given test necessarily entails inquiry as to whether the patient has recently received iodine, and it would seem that there may be scope in many cases for carrying out the test and the pre-operative preparation over largely the same period of time.

Tobacco Smoking and Nicotine Dosage

Dr. LENNOX JOHNSTON (Wallasey) writes: The answer given to questions on the injured man's "fag" (Oct. 28, p. 585) concluded "... there is no reason to withhold a cigarette from an injured man. Nicotine is a central stimulant, but in small quantities is unlikely to have either a beneficial or deleterious effect in traumatic shock." This answer supports the popular view that the dose of nicotine administered by smoking tobacco is infinitesimal or at all events immaterial. Experimental injections of nicotine, however, given to 35 volunteers and to myself indicated that "the cumulative psychic effect of a cigarette inhaled (approximately 12 inhalations) closely resembled that of nicotine gr. 1/50 hypodermically" ("Tobacco Smoking and Nicotine," Johnston, L. M., *Lancet*, 1942, **2**, 742). It was also found that nicotine gr. 1/40 and sometimes gr. 1/50 induced toxic symptoms, which included nausea, vomiting, and faintness, in non-smokers. These experiments point the conclusion that the dose of nicotine administered when a cigarette is inhaled to average depth is in the vicinity of 80% of the toxic dose—hardly a "small quantity." The faintness induced by minimal toxic doses of nicotine in healthy subjects suggests that when cardiac action is depressed, as in traumatic shock, cigarettes should be forbidden. Smokers develop a considerable degree of tolerance to nicotine. How far tolerance protects an addict against the toxic effect of his drug is, however, unknown, while it is certain that the withholding of a dose of nicotine, although causing discomfort, will do no harm. Although nicotine is a central stimulant, my experience of over 150 personal doses suggests that stimulation, which usually lasts 15 to 20 minutes following the administration of 1/50 gr. hypodermically, is followed by a similar or even longer period of depression evidenced by psychic depression and lassitude.